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# American Journal of Obstetrics and Gynecology

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## Original Communications

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### THE EFFECT OF THE INTERVAL BETWEEN BIRTHS ON MATERNAL AND FETAL OUTLOOK\*

NICHOLSON J. EASTMAN, M.D., BALTIMORE, MD.

*(From the Department of Obstetrics, Johns Hopkins University and Hospital)*

IN THE year 1925, there appeared a monograph which has probably had more influence on the pattern of childbearing in this country than any half dozen other publications. Its title was "Causal Factors in Infant Mortality, A Statistical Study Based on Investigations in Eight Cities"; its author was Robert Morse Woodbury, Ph.D., then director of statistical research in the Children's Bureau, U. S. Department of Labor. Dr. Woodbury's study is an extremely meticulous and exhaustive analysis of the more important causal agents in infant mortality; and among other factors especial attention is given to the role played by the interval of time since the preceding birth. After a careful survey of many aspects of the problem the conclusion is reached that "the infants born after short intervals had a markedly high rate of mortality from all causes. Evidently some factor that is intimately connected with the short interval—perhaps through the influence of frequent births upon the mother's health—affected adversely the chances of life of the infants who followed closely after preceding births." The specific infant mortality figures for the first year of life reported per 1,000 were as follows: for those in whom the interval

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\*Read (by invitation) at a meeting of the Chicago Gynecological Society, November 19, 1943.

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

since the preceding birth was one year, 146.7; for those in whom the interval was two years, 98.6; for the three-year-interval group, 86.5; and for those in whom the interval was four years and more, 84.9. The corresponding figures for neonatal deaths were: 51.2; 37.3; 36.7 and 38.1. Stillbirth data (p. 170) followed a similar trend. In round numbers, then, it was found that infants born after an interval of but one year following a preceding birth, faced a mortality which was one and a half times that met by infants born after intervals of two years or more. The lowest mortality for the entire first year of life was enjoyed by infants born four or more years after a previous childbirth.

Dr. Woodbury's monograph is a reserved and scholarly study, largely objective in character; and it contains no suggestion whatsoever as to what might be done to reduce infant mortality in the short interval groups. But those interested in the furtherance of birth control were quick to see a remedy. Certainly, they reasoned, if conception could be prevented in women during the first year or two after childbirth, the high mortality associated with the short interval could be prevented. And forthwith the Woodbury study became one of the cornerstones of the birth control movement and has remained so ever since. Upon it, indeed, is based the entire rationale, from a medical viewpoint, of so-called "child spacing," a term which has come to be a sort of euphemism for contraception in general. Moreover, information about this presumably high infant mortality associated with short interval births has been given such wide circulation that it is frequently stressed in our lay periodicals—always with the implication that it is a generally accepted truth, almost one of the axioms of childbearing. For instance, in the September, 1943 issue of *The Reader's Digest* an article appeared entitled "Questions on Childbirth." It starts with the challenging query, "How much do you know about the latest scientific findings as to childbirth?" Then follow a series of statements which the reader is supposed to check as "true" or "false." These comprise, in main, elementary and commonly accepted obstetric facts. Along with these, item No. 23 reads as follows: "Babies born at yearly intervals to a mother are as likely to live as if there were periods of several years between them." The answer given is: "False. Where the interval between the births of two babies is less than two years, the infant mortality rate is one and a half times as high as if the children were spaced." A footnote states, "The American Medical Association has verified the facts in this article." Here then, again, are Dr. Woodbury's figures, having reached (after approval by the American Medical Association) the *Reader's Digest* with its millions of readers.

Because of the wide influence which the Woodbury monograph has exerted, it would seem appropriate to review that portion of it which deals with the short interval problem. This comprises an analysis of

8,196 births in Baltimore, all occurring between January 1, and December 31, 1915, that is, twenty-eight years ago. In view of the many lifesaving advances which have been made both in pediatrics and obstetrics over this period, it would seem permissible to question whether conclusions drawn from births occurring in 1915 are valid today. The only other study of this type which we have been able to discover is one by Elizabeth Hughes, carried out in Gary, Indiana, in 1916. Analyzing 1,135 births (other than first births) she found that the infant mortality, under one year, was 169.1 per 1,000 live births when the interval was less than 15 months, but fell to 102.8 when the interval exceeded two years.

It is the purpose of the present communication to report an investigation based on modern material, of the effect of the interval between births on maternal and fetal outlook. The study consists of two parts. In the first, the case histories of 5,158 obstetric patients are reviewed, in all of which the interval between the previous viable delivery and the termination of the present pregnancy was accurately known and recorded on statistical punch cards. Since this portion of the investigation is based on direct knowledge of the interval between births, it may be regarded as a "direct study" of the effect of certain intervals on various maternal and fetal phenomena. In the second part of the investigation, 33,087 obstetric cases are reviewed in which the interval between births was not specifically recorded on punch cards. However, the age and parity of the patients were so recorded and by correlating these two factors (particularly great parity in younger age groups) it was possible to draw conclusions indirectly about the effect of rapid childbearing (and hence short average intervals) on maternal and fetal prognosis. This part of the investigation will be referred to as the "indirect study."

### Direct Study

The 5,158 patients in the direct study were all delivered at the Johns Hopkins Hospital between September 1, 1936 and June 30, 1943. The series was a consecutive one with the following exceptions: (1) All primiparas, of course, were excluded as were those cases in which the only previous pregnancy had terminated in an abortion. In other words, there had been in every case a previous viable delivery. (2) All cases, relatively few in number, were omitted in which the pregnancy subsequent to a viable delivery terminated in a well-attested criminal abortion. The latter group of cases would obviously vitiate any conclusions drawn in regard to the effect of the preceding interval on the *spontaneous* outcome of a subsequent pregnancy.

The distribution of the 5,158 cases according to the interval since the last viable delivery is shown in Table I, while in Table II, the various interval groups are subdivided according to race and class. It is ap-

parent from the latter table that the pattern of childbearing, that is, the extent to which births are spaced, differs considerably in the three racial and economic groups. In more than a third of the colored patients the interval since the last viable delivery was less than two years; about a quarter of the white ward cases fell into this brief interval group but only one-sixth of the private patients. In about one-half of the private patients the interval was between 25 and 48 months, suggesting that intentional child spacing is the rule among this class. It should be noted in particular that the brief interval groups are disproportionately weighted with colored patients while the longer interval groups contain relatively fewer of them. Since it is well known that both stillbirth and neonatal mortality, as well as maternal mortality, are higher in the colored race, the odds in this series are weighted somewhat against the brief interval groups.

Because the number of cases in some of the longer interval groups are too small to permit of valid statistical analysis and also for the sake of clarity, the cases have been classified in four main interval groups as shown in Table III, and henceforth, will be considered according to those categories. However, because of the great importance of the 'Very Brief' interval group for our purpose, it has been kept intact despite its

TABLE I. DISTRIBUTION OF 5,158 OBSTETRIC CASES ACCORDING TO INTERVAL SINCE LAST VIABLE DELIVERY

INTERVAL	CASES	PER CENT OF TOTAL
Less than 12 months	115	2.2
Between 13 and 24 months	1,347	26.1
Between 25 and 36 months	1,416	27.5
Between 37 and 48 months	775	15.0
Between 49 and 60 months	465	9.0
Between 61 and 72 months	284	5.5
Between 73 and 84 months	194	3.8
Between 85 and 96 months	129	2.5
Between 97 and 108 months	98	1.9
Over 9 years	335	6.5
	5,158	100.0

TABLE II. DISTRIBUTION OF 5,158 OBSTETRIC CASES ACCORDING TO INTERVAL SINCE LAST VIABLE DELIVERY AND ACCORDING TO RACE AND CLASS

INTERVAL SINCE LAST VIABLE DELIVERY	WHITE WARD		COLORED WARD		PRIVATE (WHITE)	
	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
Less than 12 mo. (1st yr.)	31	1.4	74	3.3	10	1.3
13 to 24 mo. (2nd yr.)	521	24.2	714	31.6	112	15.0
25 to 36 mo. (3rd yr.)	524	24.4	702	31.0	190	25.5
37 to 48 mo. (4th yr.)	326	15.2	272	12.0	177	23.8
49 to 60 mo. (5th yr.)	223	10.4	154	6.8	88	11.8
61 to 72 mo. (6th yr.)	170	7.9	63	2.8	51	6.8
73 to 84 mo. (7th yr.)	109	5.1	60	2.6	25	3.4
85 to 96 mo. (8th yr.)	61	2.8	47	2.1	21	2.8
97 to 108 mo. (9th yr.)	52	2.4	32	1.4	14	1.9
Over 9 years (10th yr.)	134	6.2	144	6.4	57	7.7
Total	2,151	100.0	2,262	100.0	745	100.0

small size. Fig. 1 shows the percentage composition of these four interval groups according to race and class, and directs attention again to the decreasing incidence of colored cases as the interval lengthens and the increasing frequency of white cases.

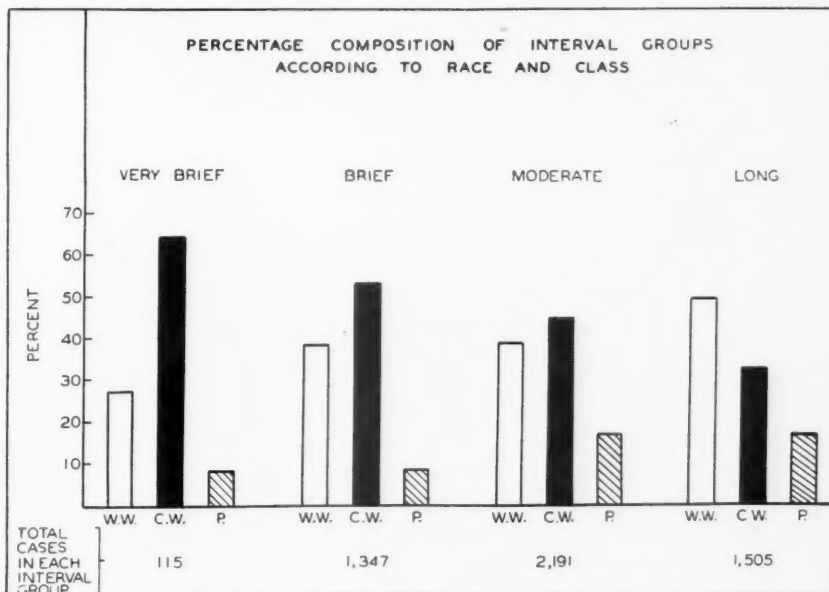


Fig. 1.—Percentage composition of the four main interval groups according to race and class. W.W. = White Ward; C.W. = Colored Ward; P. = Private.

TABLE III. DISTRIBUTION OF 5,158 OBSTETRIC CASES IN FOUR MAIN GROUPS ACCORDING TO WHETHER INTERVAL SINCE LAST VIABLE DELIVERY WAS VERY BRIEF, BRIEF, MODERATE OR LONG

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	PER CENT OF TOTAL
Very Brief—Less than 12 months	115	2.2
Brief—13 to 24 months	1,347	26.1
Moderate—25 to 48 months	2,191	42.5
Long—More than 48 months	1,505	29.2
Total	5,158	100.0

Having classified our 5,158 multiparas into four main groups according to the interval since the last viable delivery, it might seem that our only remaining task would be to analyze the percentage of infant deaths, the percentage of maternal complications and the maternal mortality in each group, and therewith the answer to our question would be at hand. Actually, the problem is much more difficult than this since the interval between births is closely correlated with certain other factors which are known to exert a most important influence on maternal and fetal outlook. Thus, the outcome for both mother and child is related to age and parity; and, naturally, women in the longer interval groups are older, as a rule, than those in the briefer interval brackets. The relative num-



ber of colored patients in each group, as already mentioned, is another possible source of error. All these complicating findings will have to be carefully weighed and, if possible, controlled in evaluating the data.

But perhaps the greatest potential source of error in this study is a certain *time element* involved in the 'Very Brief' interval group; and unless this is thoroughly understood, any conclusions drawn from this category will be totally invalid. It will be recalled that it was in this group that Woodbury found such a very high infant mortality. As shown diagrammatically in Fig. 2, if a woman is to give birth to a full-term infant within twelve months after a previous delivery, conception must take place before the end of the third month, because obviously

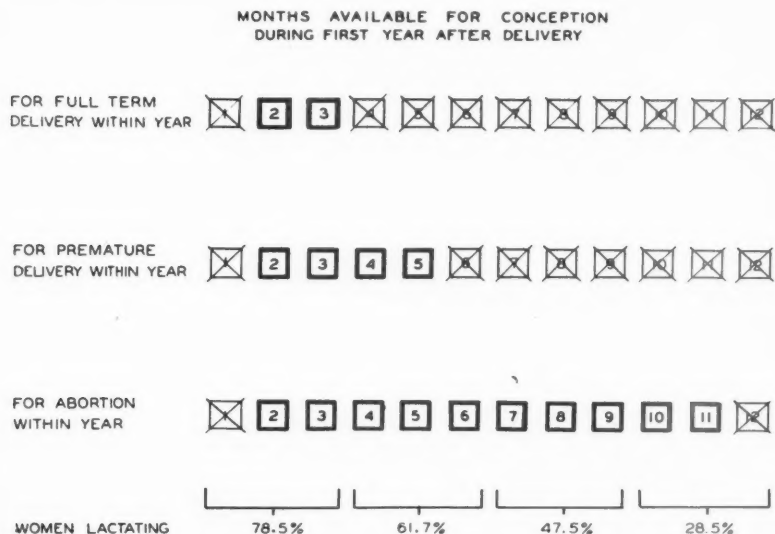


Fig. 2.—Showing that if a full-term infant is to be born within one year after a previous delivery, only two months are available for conception; but if a premature infant is to be born within the same period, four months are available; while for an abortion to take place within this interval ten months are available for conception. Below is shown the percentage of women who are lactating at various intervals after delivery and who are therefore relatively infertile.

nine calendar months are required for the development of a full-term baby. Accordingly, if we assume that ovulation does not occur within the first thirty days after delivery and in any event, that conceptions during this first month must be exceedingly rare, there are only two months in which conception can occur if a full-term infant is to be born within a span of twelve months following a previous delivery. On the other hand, in the case of premature infants, there are four months available since less time is required for the development of a premature baby. In the case of abortions, there are ten months in which a woman can conceive and abort within the year; it is, indeed, easily possible for a woman to have two abortions within twelve months after a previous delivery. Therefore, in any series of pregnancies which terminate within a year after a previous delivery, the incidence of premature deliveries

is bound to be high, possibly twice as high as usual, since there are four months available for conception and premature delivery and only two months if the subsequent delivery is to be full term. By the same token, we should expect that the relative incidence of abortion in this group would be exceedingly high. But we have reckoned thus far without considering the factor of lactation which, of course, suppresses ovulation and tends to produce temporary sterility. As the figures on the lower part of Fig. 2 indicate, fewer women are lactating in the fourth and fifth months than in the second and third, and therefore, a larger percentage are presumably fertile during the fourth and fifth months. But for a woman to conceive during these months and give birth within a year after the previous delivery, it is obviously obligatory that she go into labor prematurely. This would swell still further the incidence of premature delivery in the 'Very Brief' interval group—perhaps to two and a half or three times its normal frequency. An increase in the incidence of prematurity of this magnitude is, therefore, to be expected in this group as the inevitable result of the time element, and when confined to this magnitude, is in no way indicative of any inherent tendency of these women to have premature babies.

TABLE IV. INCIDENCE OF ABORTION IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	ABORTION	PER CENT
Very Brief—Less than 12 months	115	47	40.9*
Brief—13 to 24 months	1,347	122	9.1
Moderate—25 to 48 months	2,191	135	6.2
Long—More than 48 months	1,505	139	9.2

\*Figure not a valid index as shown in Fig. 2 and explained in text.

As was anticipated the incidence of abortion in the 'Very Brief' group (Table IV) was exceedingly high, namely 40.9 per cent. The frequency of the condition in the 'Brief' and 'Long' groups, 9.3 per cent, as compared with the incidence in the 'Moderate' group, 6.7 per cent, represents a difference which is statistically significant; but the likelihood that many of these abortions were artificially produced vitiates any conclusions which might be drawn from this complication.

TABLE V. INCIDENCE OF PREMATURE DELIVERY IN THE FOUR MAIN INTERVAL GROUPS ACCORDING TO RACE

INTERVAL SINCE LAST VIABLE DELIVERY	WHITE			COLORED		
	CASES	PREMA-TURE	PER CENT	CASES	PREMA-TURE	PER CENT
Very Brief—Less than 12 months	41	8	19.5*	74	30	40.5*
Brief—13 to 24 months	633	30	4.7	714	65	9.1
Moderate—25 to 48 months	1,217	59	4.8	974	76	7.8
Long—More than 48 months	1,005	49	4.9	500	48	9.6

\*Figure not a valid index as shown in Fig. 2 and explained in text.

Table V shows the incidence of prematurity in the four main interval groups according to race. (For the purpose of this study a premature infant is considered as one weighing less than 2,500 grams but more than 1,499 grams). This table brings out several facts: (1) The incidence of prematurity in the colored race was almost twice that in the white so that in this condition, it is obviously desirable to consider the two races separately. (2) The incidence of prematurity among white patients in the 'Very Brief' group was 4.1 times that met in the longer interval groups; and in the colored 4.7 times. Since we have estimated that the "time element" alone could account for an increased incidence of prematurity in this group of but two and a half to three times, there is a slight suggestion here that, superimposed on the time element, another intrinsic factor in these very early conceptions may be at work making for premature delivery. Additional evidence along these lines will be advanced presently. (3) In the white race the incidence of prematurity in the 'Brief,' 'Moderate' and 'Long' groups is almost identical. This means that in the white race, at least, conceptions which take place six or more months after a previous delivery stand no greater chance of terminating in premature births than those conceived after longer intervals. The same may also be true of the colored since the difference between our figures for the three groups, 9.1, 7.8 and 9.6 per cent is not statistically significant and may be due to chance. (4) If now the 'Very Brief' and 'Brief' groups are combined (thus eliminating for all practical purpose the "time element" in the 'Very Brief' group) it is apparent that the resultant percentage is higher for both races, than in the 'Brief' group taken alone. Now if, with the time element eliminated, the 'Very Brief' group had the same incidence of prematurity as the 'Brief' group, combining the two should not raise the percentage. Since it does so, we find here another suggestion that very early conceptions (before six months after a previous delivery) show a certain tendency to premature delivery.

Another suggestion that very early conceptions after a previous delivery show a greater incidence of premature birth may be adduced in another way. Consider those conceptions in this series which occurred in the fourth and fifth months. Of the 38 premature births in the 'Very Brief' interval group, it seems highly probable that at least 25 took place in these months. But, in addition, a certain number of conceptions occurred at this same period which went to term and were delivered in the first and second months of the second year. The exact number of these conceptions which terminated maturely we do not know, but we can estimate them as not more than one-sixth of the total full-term deliveries for the second year, namely 200, in round figures. This gives an incidence of prematurity for those pregnancies conceived in the fourth and fifth months post partum of 11.1 per cent, a figure which is definitely

higher than cited in Table V for the 'Brief,' 'Moderate' and 'Long' groups. Accordingly, we find suggestive evidence of three types pointing to a somewhat higher incidence of prematurity among pregnancies conceived within five months after a previous delivery. But for pregnancies conceived later than this, let us say, after the sixth month, we find no such evidence.

Tables VI, VII and VIII show the stillbirth, neonatal and total infant mortality rates in the four main interval groups. The high fetal mortality in the 'Very Brief' groups becomes understandable when it is noted that four of the five stillbirths and nine of the eleven neonatal deaths occurred in premature infants; in other words, we see here the practical effect of the "time element" expressed in terms of infant mortality. It seems probable that the same factor may have played a role in the high mortality reported in the Woodbury study for the same group, since the incidence of prematurity in the "one year interval group" of that investigation was 77 per cent higher than in the "two year interval group" (Woodbury, Table 48, page 64). In our series the stillbirth rate was identical in the 'Brief,' 'Moderate' and 'Long' interval groups, while the neonatal death rate tended to rise slightly as the interval increased.

TABLE VI. INCIDENCE OF STILLBIRTH IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	STILLBIRTHS	PER CENT
Very Brief—Less than 12 months	71	5*	7.0†
Brief—13 to 24 months	1,245	36	2.9
Moderate—25 to 48 months	2,109	63	3.0
Long—More than 48 months	1,404	41	2.9

\*Four of these five stillbirths occurred in premature infants.

†Figure not a valid index as shown in Fig. 2 and explained in text.

TABLE VII. INCIDENCE OF NEONATAL DEATH IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	NEONATAL DEATHS	PER CENT
Very Brief—Less than 12 months	71	11*	15.5†
Brief—13 to 24 months	1,245	19	1.5
Moderate—25 to 48 months	2,109	46	2.2
Long—More than 48 months	1,404	37	2.6

\*Nine of these eleven neonatal deaths occurred in premature infants.

†Figure not a valid index as shown in Fig. 2 and explained in text.

TABLE VIII. INCIDENCE OF STILLBIRTH AND NEONATAL DEATH IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very Brief—Less than 12 months	71	16	22.5*}
Brief—13 to 24 months	1,245	55	4.4 }
Moderate—25 to 48 months	2,109	109	5.2 }
Long—More than 48 months	1,404	78	5.6 }

\*Figure not a valid index as shown in Fig. 2 and explained in text.

Tables IX to XV represent a breakdown of the infant mortality figures just discussed in an effort to correct for prematurity, parity and race. Each table shows a similar pattern. The lowest mortality is met in the 'Brief' group with a slightly increasing rate in the longer interval groups, except in Table XV in which the small number of cases in the 'Long' group entails a large sampling error. As we have already

TABLE IX.—INCIDENCE AMONG MATURE INFANTS ONLY OF STILLBIRTH AND NEONATAL DEATH, IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very Brief—Less than 12 months	30	3	10.0
Brief—13 to 24 months	1,146	29	2.5
Moderate—25 to 48 months	1,966	57	2.9
Long—More than 48 months	1,302	41	3.1

TABLE X. INCIDENCE AMONG PREMATURE INFANTS ONLY OF STILLBIRTH AND NEONATAL DEATH, IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very Brief—Less than 12 months	41	13	31.7
Brief—13 to 24 months	99	26	26.3
Moderate—25 to 48 months	143	52	36.4
Long—More than 48 months	102	37	36.3

TABLE XI. INCIDENCE AMONG PARA II ONLY OF STILLBIRTH AND NEONATAL DEATH IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very Brief—Less than 12 months	36	9*	25.0†
Brief—13 to 24 months	520	17	3.3
Moderate—25 to 48 months	816	28	3.4
Long—More than 48 months	497	19	3.8

\*Six of these nine deaths occurred in premature infants.

†Figure not a valid index as shown in Fig. 2 and explained in text.

TABLE XII. INCIDENCE OF STILLBIRTH AND NEONATAL DEATH, *White Only*, IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very Brief—Less than 12 months	23	5	21.7
Brief—13 to 24 months	574	20	3.5
Moderate—25 to 48 months	1,161	46	4.0
Long—More than 48 months	940	42	4.5

TABLE XIII. INCIDENCE OF STILLBIRTH AND NEONATAL DEATH, *Colored Only*, IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very Brief—Less than 12 months	48	11	22.9
Brief—13 to 24 months	671	35	5.2
Moderate—25 to 48 months	948	63	6.6
Long—More than 48 months	464	36	7.8



stressed, it is our opinion that the high mortality in the 'Very Brief' interval group is largely the result of the high percentages of prematurity in this group due to the inescapable "time element."

Turning now to the effect of the interval between births on maternal outlook, Table XVI shows that there is no significant difference between the incidence of anemia in the 'Brief,' 'Moderate' and 'Long' groups. The figures for the 'Very Brief' group are too small to warrant conclusions.

TABLE XIV. INCIDENCE OF STILLBIRTH AND NEONATAL DEATH, *Para II, White Only*, IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very brief—Less than 12 months	13	2	15.4
Brief—13 to 24 months	286	5	1.7
Moderate—25 to 48 months	551	11	2.0
Long—More than 48 months	358	9	2.5

TABLE XV. INCIDENCE OF STILLBIRTH AND NEONATAL DEATH, *Para II, Colored Only*, IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very Brief—Less than 12 months	23	7	30.4
Brief—13 to 24 months	234	12	5.1
Moderate—25 to 48 months	265	17	6.4
Long—More than 48 months	122	5	4.1

TABLE XVI. INCIDENCE OF MATERNAL ANEMIA\* DURING PREGNANCY IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	WHITE ANEMIA	PER CENT	CASES	COLORED ANEMIA	PER CENT
Very Brief—Less than 12 months	16	4	25.0	29	10	34.5
Brief—13 to 24 months	438	55	12.6	520	144	27.7
Moderate—25 to 48 months	781	102	13.1	742	236	31.8
Long—More than 48 months	675	88	13.0	393	94	23.9
Total	1,910	249	13.0	1,684	484	28.7

\*By anemia is meant less than 10 grams of hemoglobin per 100 c.c. of blood, i.e., less than 70 per cent.

TABLE XVII. INCIDENCE OF TOXEMIA OF PREGNANCY (ALL TYPES) IN THE FOUR MAIN INTERVAL GROUPS, ACCORDING TO RACE AND CLASS

INTERVAL SINCE LAST VIABLE DELIVERY	WHITE WARD			COLORED WARD			PRIVATE		
	CASES	TOX-EMIA	PER CENT	CASES	TOX-EMIA	PER CENT	CASES	TOX-EMIA	PER CENT
Very Brief Less than 12 months	19	4	21.1	45	7	15.6	4	0	0.0
Brief 13 to 24 months	465	55	11.8	655	144	22.0	105	3	2.9
Moderate 25 to 48 months	794	137	17.3	918	230	25.1	344	19	5.5
Long More than 48 months	688	139	20.2	453	140	30.9	235	19	8.1
Total	1,966	335	17.0	2,071	521	25.2	688	41	6.0

One of the most striking effects of the interval between births encountered in this study is in the incidence of toxemia of pregnancy (pre-eclampsia, eclampsia and chronic hypertensive vascular disease combined). It seems clear from Table XVII that in each of the three racial and economic groups considered, the incidence of toxemia increases decidedly as the interval increases. (The high figures for toxemia in both the white and colored ward groups is due to the fact that the ward service is a consultation center for nineteen prenatal clinics scattered throughout Maryland. Our ward population is, therefore, not a representative cross section of the population at large either white or colored). Likewise, as shown in Table XVIII, the incidence of "repeat toxemias" increases with prolongation of the interval. This latter fact has already been demonstrated by Chesley and his associates.

TABLE XVIII. INCIDENCE OF "REPEAT" TOXEMIA IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIALE DELIVERY	CASES	TOXEMIA	PER CENT
	TOXEMIA PREVIOUS PREGNANCY	SUBSEQUENT PREGNANCY	
Very Brief—Less than 12 months	15	7	46.7
Brief—13 to 24 months	264	107	40.5
Moderate—25 to 48 months	431	191	44.3
Long—More than 48 months	190	98	51.6
Total	900	403	44.8

There was no significant difference between the incidence of post-partum hemorrhage or of puerperal fever in the four main interval groups. (Tables XIX and XX).

TABLE XIX. INCIDENCE OF POST-PARTUM HEMORRHAGE\* IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIALE DELIVERY	CASES	HEMORRHAGE	PER CENT
Very Brief—Less than 12 months	68	0	0.0
Brief—13 to 24 months	1,225	30	2.4
Moderate—25 to 48 months	2,056	88	4.3
Long—More than 48 months	1,376	47	3.4
Total	4,725	165	3.5

\*By post-partum hemorrhage is meant blood loss of 600 c.c. or more.

TABLE XX. INCIDENCE OF PUERPERAL FEVER IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIALE DELIVERY	WHITE			COLORED		
	CASES	FEVER	PER CENT	CASES	FEVER	PER CENT
Very Brief Less than 12 months	23	2	8.7	45	10	22.2
Brief 13 to 24 months	570	48	8.4	655	147	22.4
Moderate 25 to 48 months	1,138	114	10.0	918	196	21.3
Long More than 48 months	923	90	9.7	453	93	20.5
Total	2,654	254	9.6	2,071	446	21.5

The ability to nurse the baby without supplementary feeding, is usually taken as indicative of a healthy maternal state. Table XXI shows that, with the exception of the 'Very Brief' group, the incidence of breast feeding only was the same in all the interval groups. The high percentage of premature babies in the 'Very Brief' group accounts presumably for the high frequency of artificial feeding in this category. The mean birth weight of the mature babies and their mean weight gain in the hospital, in respect to their birth weight, showed no substantial differences. (Table XXII).

TABLE XXI. INCIDENCE OF BREAST FEEDING ONLY IN THE FOUR MAIN INTERVAL GROUPS ACCORDING TO RACE AND CLASS

INTERVAL SINCE LAST VIALE DELIVERY	WHITE WARD			COLORED WARD			PRIVATE		
	CASES	B.F.	PER CENT	CASES	B.F.	PER CENT	CASES	B.F.	PER CENT
Very Brief									
Less than 12 months	19	7	36.8	48	13	27.1	4	0	0.0
Brief									
13 to 24 months	469	326	69.5	671	447	66.6	105	55	52.4
Moderate									
25 to 48 months	812	516	63.5	948	679	71.6	349	183	52.4
Long									
More than 48 months	702	462	65.8	464	290	62.5	238	104	43.7
Total	2,002	1,311	65.5	2,131	1,429	67.1	696	342	49.1

TABLE XXII. MEAN BIRTH WEIGHT OF MATURE INFANTS (2,500 GRAMS AND OVER) AND MEAN WEIGHT GAIN IN HOSPITAL, IN RESPECT TO BIRTH WEIGHT, OF BREAST-FED MATURE INFANTS, IN THREE MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIALE DELIVERY	CASES	MEAN BIRTH WEIGHT	MEAN WEIGHT GAIN
Very Brief—Less than 12 months	1,316	3,355 grams	11.8 grams
Brief—13 to 24 months		3,411 grams	31.7 grams
Moderate—25 to 48 months		3,407 grams	29.5 grams
Long—More than 48 months	1,404	3,407 grams	29.5 grams
Total	4,829	3,395 grams	19.5 grams

Finally, in the direct study, the maternal mortality in the four main interval groups was essentially the same. (Table XXIII).

TABLE XXIII. MATERNAL MORTALITY IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIALE DELIVERY	CASES	DEATHS	PER CENT
Very Brief—Less than 12 months	115	0	0.00
Brief—13 to 24 months	1,347	3	0.22
Moderate—25 to 48 months	2,191	7	0.32
Long—More than 48 months	1,505	6	0.40
Total	5,158	16	0.31

### Indirect Study

The rationale of the indirect study is as follows: It is well known that fetal mortality varies with both parity and age, as shown in Figs. 3 and 4. Now if, instead of plotting total fetal mortality by age, as done in Fig. 4, we plot only the fetal mortality of para ii by age, we do

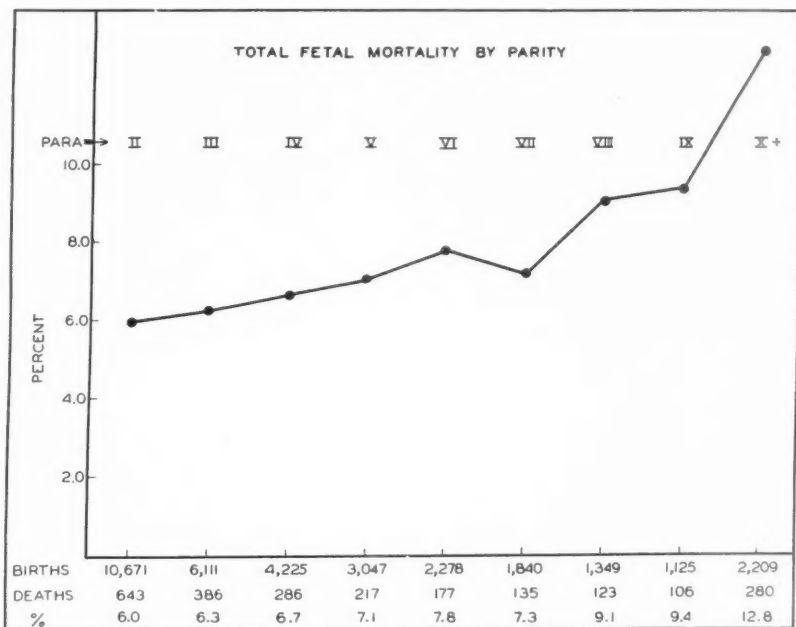


Fig. 3.—The upward trend of fetal mortality (stillbirth and neonatal) with increasing parity. (Primipara omitted).

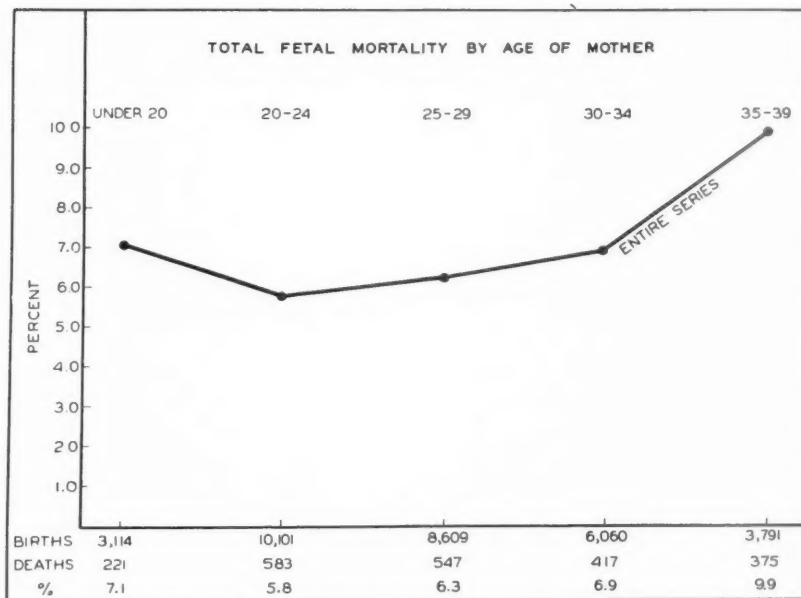


Fig. 4.—The curve of fetal mortality (stillbirth and neonatal) according to age of mother.

away with variations caused by parity and can ascertain fetal mortality in any age group in women of this particular parity. The resultant curve (marked para ii) is plotted in Fig. 5. From this we learn, for instance, that for para ii, ages 20 to 24, the fetal mortality is 5.5 per cent; and for para ii, ages 25 to 29, 5.1 per cent. Now let us superimpose on this graph the fetal mortality curve of para iv by age. Since women with a parity of iv have a higher fetal mortality than those with a parity of ii (as shown in Fig. 3), the curve of the para iv group will naturally fall at a somewhat higher level. However, provided there are no other factors at work affecting fetal mortality in one age group more than another, the two curves should be parallel. As shown in Fig. 5, these two curves do run approximately parallel in our series.

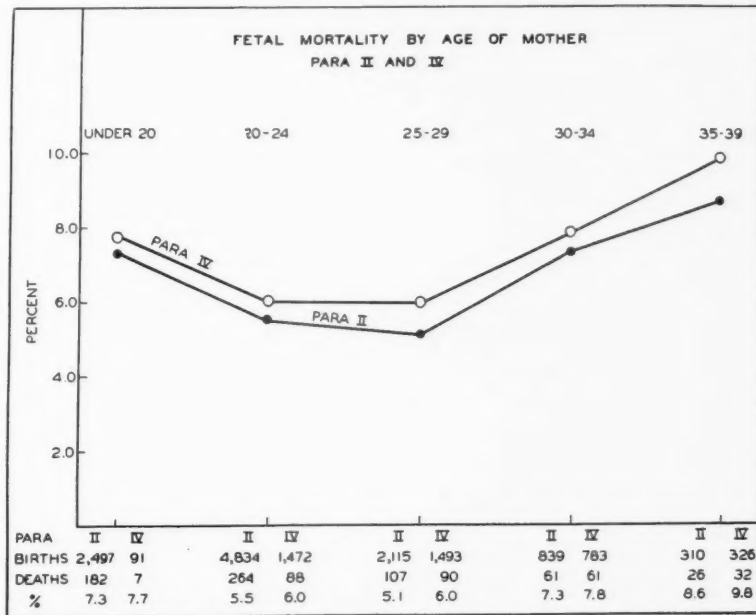


Fig. 5.—The curve of fetal mortality (stillbirth and neonatal) according to age of mother, para ii and para iv only.

Let us now consider the age groups (para ii and iv) ages 20 to 24. Obviously in any large aggregation of cases such as this, women who have had four babies before age 24 have had on the average a shorter interval between births than those who have had only two before age 24. We can conclude, then, indirectly that the para iv, ages 20 to 24 represent a shorter interval group than para ii, ages 20 to 24. Now if the shorter interval between births characteristic of the para iv, ages 20 to 24, exerted a deleterious effect on fetal mortality, it should cause a deviation upward of the mortality curve at this point. Actually no such deviation is encountered. Moreover, the graph shows that a woman who is giving birth to her fourth child between 20 and 24 experiences



no greater fetal mortality than the woman who is being delivered of her fourth infant between 25 and 29, although obviously in any large series the average interval between births in the latter age group would be greater.

If this type of analysis is pressed further and the mortality curve of para v is superimposed on that of para ii (Fig. 6), we find that the curve is at a still greater level above that for para ii (due to the higher mortality rate associated with this greater parity group), but there is clearly no deviation from the parallelism seen in Fig. 5. Obviously, a woman who has had five children at the age of 24, has experienced, on the average, shorter intervals between births than one who has had only

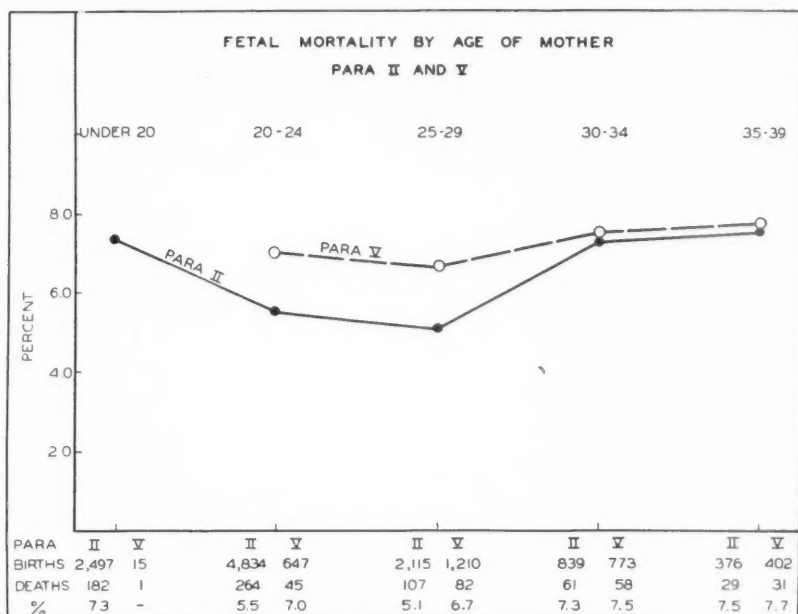


Fig. 6.—The curves of fetal mortality (stillbirth and neonatal) according to age of mother, para ii and para v, only.

two children at that age. But except for an increased mortality due to greater parity, an increase that is proportionate to that observed in other age groups, we find no difference in infant mortality between the para v of 24 and the para ii of the same age. It will be noted, furthermore, that the woman who is having her fifth baby between 20 and 24 faces substantially the same infant mortality as one who is giving birth to her fifth baby between 25 and 29.

In sum, our indirect study has failed to indicate that rapid multiparity, with an average short interval between births, exerts any appreciable effect on infant mortality.

In Fig. 7 similar graphs of infant mortality plotted according to age are shown based on data compiled in New York State (exclusive of New

York City) by Dr. Jacob Yerushalmy, Medical Statistician, U. S. Public Health Service. His findings in regard to para ii and para iv are strikingly similar to ours. His para v group, however, does show a marked upward swing in the 20 to 24 age group, suggesting a harmful effect exerted by rapid multiparity. Both Dr. Yerushalmy's figures and ours in this particular parity and age group are based on less than 1,000 cases and the discrepancy may be due to a sampling error in one or the other series.

Finally, in the indirect study, the maternal mortality of para ii as compared with that of para iv, v and vi (grouped) was in any age group essentially the same. (Table XXIV).

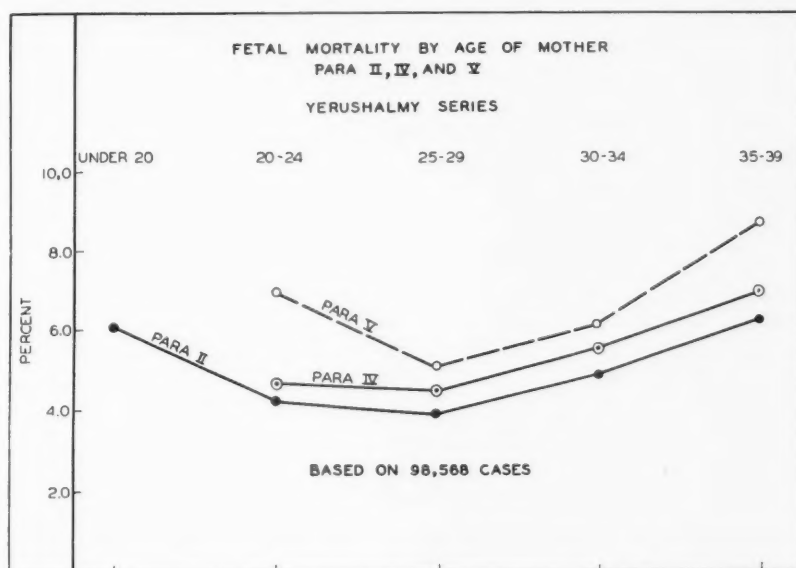


Fig. 7.—Fetal mortality according to age of mother, para ii, iv and v, based on data compiled by Dr. Jacob Yerushalmy.

TABLE XXIV. MATERNAL MORTALITY OF PARA II COMPARED WITH THAT OF PARA IV, V AND VI (GROUPED), ACCORDING TO AGE

	UNDER 20	20 TO 24	25 TO 29	30 TO 34	35+
Para II					
Cases	2,479	4,797	2,092	839	372
Deaths	6	13	4	8	3
Per cent	0.24	0.27	0.19	0.95	0.81
Para IV, V and VI					
Cases	107	2,358	3,493	2,200	1,210
Deaths	0	6	8	17	12
Per cent	0.00	0.25	0.23	0.77	0.99

### Summary and Conclusions

When the data reviewed in this study are analyzed from the viewpoint of their statistical validity, it becomes clear that certain of the findings are significant beyond question, while others are only on the borderline

of statistical significance and hence must be regarded as suggestive only. In the former category the following conclusions seem clear-cut and inescapable: (1) Infants born from twelve to twenty-four months after a previous viable delivery (that is, during the second year) have at least as low a stillbirth and neonatal mortality as do infants born after longer intervals. (2) The longer the interval between births, the more likely the mother is to suffer from some form of hypertensive toxemia of pregnancy. The incidence of this complication is lowest when the interval is twelve to twenty-four months, significantly higher when it is twenty-four to forty-eight months, and much higher when it exceeds four years. In the present study this was equally true of white and colored ward and private patients. (3) In patients who have had a previous hypertensive toxemia of pregnancy, the likelihood of repetition becomes progressively greater as the interval becomes longer. (4) The incidence of the following conditions is no greater when the interval is twelve to twenty-four months than when it is longer: premature labor, anemia, post-partum hemorrhage, and puerperal infection; nor are mothers in this brief interval group less able to nurse their babies. The weight of the mature babies was approximately the same regardless of the interval.

Among those findings in the study which are on the borderline of statistical significance, the trend in the neonatal mortality is perhaps the most suggestive. This was 1.5 per cent for the 'Brief' interval group, 2.2 per cent for the 'Moderate' group, and 2.6 per cent for the 'Long' group. The difference between the first two of these percentages is 1.5 times the standard error of the difference; in other words, the odds are about 6 to 1 against the likelihood that this difference is due to a sampling error. The difference between the first and third of these percentages is 2.0 times the standard error of the difference; in other words, the odds are about 20 to 1 against the chance that this difference is due to a sampling error. When it is further recalled that hypertensive toxemia of pregnancy increases progressively in each of these three groups and that this complication is a frequent cause of premature delivery and hence neonatal death, the upward trend in our neonatal mortality as the interval increases becomes all the more plausible. But let it be emphasized again that our figures do not prove it, but merely suggest the probability.

Most tenuous of all inferences to be drawn from this study are those which have to do with the 'Very Brief' interval group. Not only is the number of cases in this group very small, but other difficulties in analysis present themselves, particularly the time element. While we feel sure that this time element accounts in large measure for the high incidence of abortion and premature labor in this group, we cannot be sure that it is wholly responsible; and, as indicated, there is suggestive evidence that pregnancies which are conceived within five months after a previous delivery show a slightly higher incidence of premature termination.

Finally, concerning the bearing of our findings on the practical issue of child spacing, the following question would seem permissible. In recommending child spacing for the health of mother and infant, have we not overlooked the greatest talisman that a pregnant woman can possess, namely, Youth? Child spacing, by definition, means maternal aging; and after a certain optimum period, probably in the early twenties, maternal aging means inevitably somewhat higher risks both to mother and child. All experience and all statistics support this statement. It would seem almost inconceivable that a mere difference in age of four years or so could have any appreciable effect on the outcome of childbearing, yet in any considerable series such as this, it manifests its influence unmistakably; and whatever advantage is gained by a rest period of several years between births seems to be offset, and in some respects more than counterbalanced by the aging factor. For the best maternal and fetal outlook we are inclined to believe that Youth is a better ally than child spacing.

The author is greatly indebted to Dr. Jacob Yerushalmy, Medical Statistician, U. S. Public Health Service, for advice and active help in the preparation of the statistical data presented in this paper. However, the interpretation of the data and the conclusions drawn are solely the responsibility of the author.

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### Discussion

DR. WILLIAM J. DIECKMANN.—Dr. Eastman has made a very thorough study of an important subject about which little is known. He could have drawn various sensational conclusions, but he has simply pointed out that his critical group, namely, those with an interval of one year, was too small for wide comparisons.

Adair mentions that the minimum time between labors should be 18 months. Sellheim states that pregnancy, lactation, and involution and regressive changes each require nine months. He suggests, therefore, that the proper spacing is three years between labors. He stated that the second and third babies had a lower mortality than the first but the fetal mortality steadily increases after the third. The Metropolitan Life Insurance Company reports that there is a slightly lowered mortality for married women between 25 and 45 than for single. Isenhour and co-workers studied blood pressure levels in parous and nulliparous women from 20 to 60 plus years. No difference could be noted in the incidence of hypertension and average blood pressure levels of these two groups of women. They stated that hypertension following a toxemia of pregnancy is not the result of this complication of pregnancy, but rather that toxemia occurs most frequently in patients with predisposition for vascular disease.

I have always taught that the interval between pregnancies should be two years, but for the past eight years, where the patient had sufficient income to provide proper

food, private care, and some help at home, I have told the patient that she may have another baby within 12 to 18 months. I was influenced in my change by several women who deliberately had their babies, two or three, as close as possible. Their reasons were that they wished the "diaper stage" at one time, that their activities already restricted by one baby would not be further affected by more, and finally, that the children with a short interval between were better companions for each other.

In clinic patients, I have been studying the blood, as well as the renal function, heart size, etc., in patients who have had ten or more children. I do not believe that pregnancy causes injury to the normal woman. I have one patient who in 1942, when 46 years old, had her seventeenth baby. There were no abortions and only one baby died. These 17 pregnancies occurred in a period of 26 years. We delivered the last seven babies, the final two pregnancies being complicated by hypertension. Obviously this patient now has an essential hypertension resulting from her age and a predisposition for vascular disease.

Woodbury's study is based on a very low income group and is, therefore, not applicable to general maternal and fetal complications and mortality.

Eastman reports that the premature mortality in his group with less than a year between pregnancies was relatively high, but that the number is too small for definite conclusions. He could find no difference for anemia, although I would expect such to exist. Post-partum hemorrhage and puerperal infection showed no change as one would expect. He emphasizes that the incidence of toxemia increases with each longer interval.

We have just completed a study of 490 toxemic patients who had two or more viable babies in our hospital. With intervals of two years, three to four, five to six, and seven to eight years, the incidence of recurrence of toxemia was 37 per cent in the first group, 47 in the second, 60 in the third, and 64 per cent in the last. Our data also show that with increasing age, the incidence of recurrence of toxemia increases. Obviously, patients who had a toxemia of pregnancy should not wait two or more years before the next pregnancy.

I have been stating for a number of years that many patients have a predisposition to vascular disease which first manifests itself in pregnancy. Furthermore, I have pointed out that if a patient has a toxemia in one pregnancy and then is found ten years later to have a hypertension, the probabilities are that the vascular disease is simply the result again of age plus a predisposition. It is pleasing to have confirmation of this from Eastman's study as well as from Stander's clinic.

Eastman's final sentence, which I most heartily endorse, is "For the best maternal and fetal outlook we are inclined to believe it is better to rely on Youth than on Child Spacing."

DR. WILLIAM C. DANFORTH.—It is remarkable how an error once published, is quoted and repeated indefinitely. The study to which we have just listened has clearly shown how failure to evaluate all the facts may lead to wrong conclusions. In carefully analyzing his figures, and in drawing the proper conclusions from them, Doctor Eastman has done us a service and it is to be hoped that his results may attain their deserved publicity.

The work which has been presented here tonight is timely. We are engaged in a great war in which the wastage of life cannot fail to be great. The need for the replacement of those who do not return will soon be felt. It is important, too, that the replacement should come from that part of the people which is capable, physically and mentally, of producing a new generation which will be able to cope with the problems of the future.

As I cannot question either the accuracy of Doctor Eastman's figures or the validity of the conclusions he draws, I beg leave to take a moment to point out a



further implication of this work. As Doctor Eastman has said, the advocates of birth control were quick to seize upon the conclusions of Woodbury.

Birth control, child spacing or planned parenthood, all of which mean the same thing, are concerned with the problem presented by the individual family. As physicians, as men whose lifework is the management of the reproductive process and the ills peculiar to women, and as citizens who have enjoyed more than the average opportunity for the acquisition of knowledge concerning social and community problems, it seems to me that we should look further than this. While conceding that the individual woman may be benefited, what is the result upon the nation as a whole? It has been my experience that the most eager searchers after information concerning contraception are those of the upper intellectual and economic levels. Families among these, the more responsible of our citizens, are limited while far less limitation is found among the irresponsibles and the less efficient. What will be the long range effect upon the country of limited reproduction among those who may logically be expected to produce the best quality of offspring?

Statisticians tell us that a minimum of three children per family is needed to maintain the population at a given level. This is true today with our greatly improved methods of infant care. One hundred years ago, six were needed. If we regard the number of births needed to maintain population at its present level as represented by 100, it is shown by Dublin that, during the time represented by the years 1935 to 1940, the net urban reproduction rate was only 74 per cent. During this same period the rural rate was 144 per cent. The average rate was 96 per cent. Part of this rural excess was in backward parts of the country, in which education and even nutrition were defective. In these areas stock of less than full value was produced. The 96 per cent, therefore, is scarcely worth its face value. We have not as yet attained the low rates found in other countries, as for example, 74 per cent in England and Wales in 1933, but any rate of reproduction which is less than enough to maintain the population level cannot be looked upon as a sign of national health. Had not the decline in the birth rate in the last century been accompanied by a marked decline in the death rate, the result would have been serious.

The statistical studies of Dublin also show that much of the upswing of births in the past two years has taken place in first and to a lesser degree, in second, births. This is only slightly evident in third births and from that point on, the decline continues. The present increase in the birth rate must be regarded as temporary and occasioned by the wave of marriages caused by the outbreak of war.

It is important to society as a whole that the lives and the health of women be protected. They are the producers of children, they bring up the children and have the greatest part in their early training and they are the centers of the homes. There is no class of citizens more valuable to the country than women of childbearing age. Anything which renders the giving of this service safer and pleasanter is worthwhile, not only to them but to all of us. But, in order that the desires of each individual family shall be consulted as to the number, usually a small one, of the children which they shall have, let us not lose sight of the extremely important question of the production of the next generation of our national family. It will require but a few generations insufficient in numbers to cause a marked decrease in the population as a whole. But a few generations in which the reproduction has been largely in the ranks of those of lesser intelligence and physical vigor will stunt the mental and physical strength of the nation, perhaps to a dangerous extent. The need for waging two great wars within the space of one generation should warn us that this is a dangerous prospect. It has been said that birth control gives us the power to determine not only the size but the character of the nation. Such figures as have been published concerning the reproduction rates of college men and women, for example, give but little cause to exult over the influence it exercises over the character,

The evidence presented here tonight shows that, apart from the very brief group, in which premature deliveries vitiate the fetal mortality figures, neither the fetal nor the maternal mortality is materially affected. This should remove some of the fears which some, at least, in this country have had, that the having of a fair sized family is a menace. It is indeed youth upon which we must rely rather than upon child spacing.

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**Adam, G. Shedden:** *The Rh Factor and Its Application to Obstetric Practice*, M. J. Australia 1: 507, 1943.

The author reviews the history of the Rh factor in relationship to blood transfusion, and stresses its importance in obstetric practice. In obstetrics the chief point of consideration is the concept of iso-immunization in the human body by the Rh factor. This has thrown new light on the etiology of erythroblastosis fetalis. In regard to blood transfusion, if the woman requires a blood transfusion during her pregnancy or puerperium, it is best not to use the husband for the donor even though he is of the same blood group. It is advised that stocks of serum containing the anti-Rh factor be built up. In transfusing a baby with icterus gravis neonatorum, the mother's blood should not be used since the body is almost certainly "Rh positive" and the mother's blood contains the Rh antibody which will only destroy more of the infant's red cells. The father is also not a suitable donor for his red cells would be destroyed by the presence of the Rh antibody (acquired from the mother) in the infant's serum. The most suitable donor is obviously one whose blood is "Rh negative" and does not contain the Rh antibody.

WILLIAM BERMAN.

**Young, James:** *Maternal and Child Health: The University and the Public Health Services*, Edinburgh M. J. 50: 474, 1943.

Dr. Young outlines in this article the planning of the future services which concern the health of the mother and child. He states these plans require the necessity of making arrangements for the training of doctors, consultants, nurses, health visitors and social workers who will be responsible for maternal and child welfare.

These arrangements include, (1) the establishment of adequate departments of maternal and child health in the medical schools and universities, (2) intimate collaboration between these departments of maternal and child health and the maternity and child welfare and school medical services of the health authorities.

The author stresses the fact, too often overlooked and neglected in this country, that *organizations of services designed to give adequate care to mother and child must be so developed as to provide a continuity of supervision from the prenatal period to school age.*

CLAIR E. FOLSOME.

## THE BIOLOGIC CHARACTERISTICS OF THE NORMAL VAGINA\*†

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### Introduction

IT IS now generally conceded that the biologic characteristics of the normal human vagina during the sexually mature period of life are governed by the ovarian hormones. It has been established beyond doubt that the estrogens are the primary factors responsible for the proliferation of the vaginal epithelium, and there is also very good evidence that, in the human and in the monkey, it is the estrogens which mediate the deposition of glycogen in the vaginal epithelial cells. Progesterone appears to play some part in the further differentiation of these cells and possibly also influences some of the biochemical characteristics of the vaginal tract, but the evidence on this score is still meager. Beyond this, much controversy continues to exist on the mechanism by which the vaginal glycogen is metabolized and on the origin and nature of the enzymes involved in the fermentation of the carbohydrates to acid. The same uncertainty also exists as to whether the lactic acid, which is responsible for at least most of the vaginal acidity, is produced as an end product in this enzymatic process or whether the conversion of carbohydrates to lactic acid results from the action of certain bacteria particularly the lactobacilli of Döderlein. Nor is it yet settled that these biochemical reactions determine the type of flora which can inhabit the vagina or whether the converse is true, namely, that the presence of certain organisms in the vaginal tract will strongly influence certain of the biochemical reactions of the vagina.

To these problems have recently been added the difficulties of defining subtle but yet important alterations in the vagina occurring rhythmically in association with the ovarian cycle. Such periodic differences in the histology and cytology of the vagina are now quite generally accepted, and data are accumulating on similar cyclic variations in some of the normal biochemical characteristics such as glycogen content and vaginal acidity.

\*Read at a meeting of the Philadelphia Obstetrical Society, October 7, 1943.

†This work has been supported by a grant from the Johnson Research Foundation. We are indebted to Dr. Norris W. Vaux for the facilities of his department, his continuous interest in our work, and his many helpful suggestions.

These problems assume more than theoretical significance when one attempts to define the normal vagina and to establish various abnormal or pathologic states upon this basis. It is apparent that, in order to do this, certain criteria based upon well-founded observations must be available by which it will be possible to evaluate at least those factors which may be of clinical significance. Scattered observations on various of these factors in normal patients have been made by many observers, but, unfortunately, little attempt has been made to correlate the various factors in the same patients. In the process of making such routine studies on large numbers of patients, we have accumulated a considerable amount of data on the various biologic factors of the normal vagina. These form the basis of the observations which are here presented in conjunction with a rather detailed discussion of pertinent data in the literature as a critical analysis of what constitute the biologic characteristics of the normal vagina.

#### Selection of Patients

It was considered important that the patients selected for this study should be in general good health. Patients with malnutrition, vitamin deficiencies, and other metabolic disturbances were not chosen since these factors may have an important bearing on the health of the vagina not only by their effect on mucous membrane in general, but also because they may influence ovarian function. Patients with any endocrine disturbances, particularly those involving the pituitary-ovarian cycle and also those with thyroid disease, were avoided for similar reasons.

It was also required that the menstrual cycle should be reasonably normal. Those patients were chosen in whom the menses recurred regularly at intervals of 26 to 30 days with a flow of from 3 to 7 days and who had an approximately normal amount of bleeding. A pelvic examination was also made to rule out any gross abnormalities of the uterus and adnexa. Moderate malpositions of the uterus were overlooked as having little significance. The patients were carefully questioned to rule out the presence of symptoms suggesting any vaginal abnormalities such as excessive discharge, local irritation, burning, itching, heat, dyspareunia, and dysuria. It was required also that the patients should not employ any local treatment or medicaments such as douches, jellies, suppositories, and the like. Patients were asked to refrain from coitus for 24 hours preceding examination. These patients had no knowledge of contraceptive measures or did not employ them except for the practice of withdrawal.

A thorough examination of the lower genital tract was made at each visit as follows: The vagina was exposed with a bivalve speculum, without the use of a lubricant, and the vagina and cervix were then carefully inspected for the presence of any abnormalities, particularly with respect to evidences of irritation, inflammation, ulceration, or erosion.

The vaginal and cervical discharges were then carefully inspected and a note made concerning the amount, color, consistency, character and odor. The special studies which were then made included determinations of the pH of the vaginal mucosa at several levels; the preparation and examination of vaginal smears for cytologic study, glycogen content, and bacterial flora; examination of fresh wet vaginal smears for parasites and cellular content, and the removal of small vaginal biopsies for routine histologic study and special glycogen stains. The details of the methods employed for these studies will be given separately as each factor is discussed.

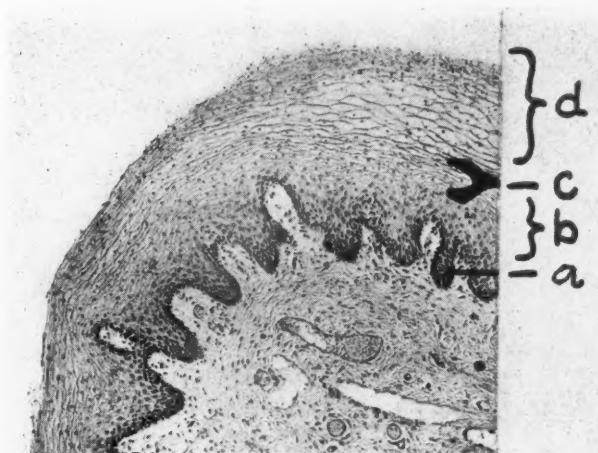


Fig. 1.—Normal vaginal mucosa.  
 (a) Dark zone of basal  
 (b) Light zone of basal  
 (c) Dierks' intraepithelial zone of cornification  
 (d) Superficial or functional layer

We have accumulated such data on more than 500 patients; however, there were only 37 normal patients among these in whom we were able to obtain satisfactory studies 3 times weekly through one to three menstrual cycles. These latter form the basis for most of the normal values herein presented.

### I. The Endocrine Factor

In order to fully appreciate the influence of the ovarian hormones on the vaginal mucosa, it is necessary to be fully familiar with the histologic characteristics of this structure. This may best be described in terms of the normal as it occurs in the sexually mature female (Fig. 1).

The vaginal epithelium is supported upon a thick, well-developed, connective tissue layer or tunica propria, rich in small blood vessels and lymphatics. Just beneath the fine basement membrane (lamina propria), small numbers of leucocytes are present which are generally of the lymphocytic and monocytic series. A moderate variation in the number



of leucocytes in the subepithelial layer occurs throughout the cycle, but aggregations of large numbers of these cells are abnormal, often being one of the earliest findings of an inflammatory lesion of the vagina. The vaginal epithelium itself consists of a number of layers some of which are inconstant and have been variously indicated by different observers. The deepest layer is generally referred to as the basalis and is made up of one or more rows of deeply staining cells (the "dark zone") and a larger number of rows of less compact cells with weaker affinity for the basic stain (the "light zone"). The dark zone may consist of a ribbon of deeply staining cuboidal cells with large dark nuclei, or, in some phases of the cycle during which rapid growth is occurring, it may consist of several rows of such cells. In the light zone of the basalis, the shape of the cells changes as they progress upwards from oval to polygonal to a flat spindle contour. Sharply dividing the basalis from the most superficial layer is a thin dense layer which is not constantly present and which is commonly referred to as Dierk's "intra-epithelial zone of cornification."<sup>1</sup> The cells here are markedly compressed, and the nuclei are also flattened and stained deeply. Within the cells and also in the intracellular spaces are numerous granules of various sizes which impart a characteristic appearance to this layer. The superficial layer above this, commonly referred to as the "functionalis," consists of a varying number of rows of stratified cells which have undergone cornification to a greater or lesser extent. When stained by appropriate methods, the cells of all layers, except the dark zone of the basalis, are found to be rich in glycogen.

### Estrogen Effect

Although some of the earlier German workers hinted at a relationship between ovarian activity and the biologic characteristic of the vagina, the first definite description of such a correlation is generally attributed to Muir<sup>2</sup> who arrived at his conclusions from purely clinical studies. These observations were soon corroborated and further expanded by many workers particularly by Cruickshank and Sharman.<sup>3</sup> The latter demonstrated that, in those periods of life associated with high estrogen levels, namely, in newborn infants up to the third or fourth week of life and in women during the reproductive period, there is a deep many-layered vaginal epithelium rich in glycogen; whereas, in the periods of diminished ovarian function, namely, in childhood and following the menopause, the vaginal epithelium is thin, and glycogen is absent. Cruickshank and Sharman further correlated those periods of high estrogen concentration with a strongly acid secretion and a homogeneous bacterial flora and pointed out that this was particularly true during the latter months of pregnancy where there is an overabundance of estrogen.

The role of the estrogens in inducing proliferation of the vaginal epithelium was described in castrate monkeys by Allen<sup>4</sup> and in female children by Lewis<sup>5</sup> and, subsequently, has been confirmed by numerous

other workers. As the result of the injection of estrogens an enormous growth in the vaginal epithelium can be induced. In spayed monkeys and in postmenopausal women, the few cell layers present may be made to increase to as many as 60 or 80 rows. As pointed out by Allen, one of the first things that is noted as the vaginal epithelium thickens is the increased number of growing bulbs along the basement membrane, the cells of which contain many mitotic figures. The nuclei of the intermediate layers become pyknotic. Sometimes, remnants of nuclei may also be found in the superficial layer, but, more often, these cells are completely cornified although not to so marked a degree as in the rodents. Comparable observations may be made in human vaginal biopsies (Fig. 2).

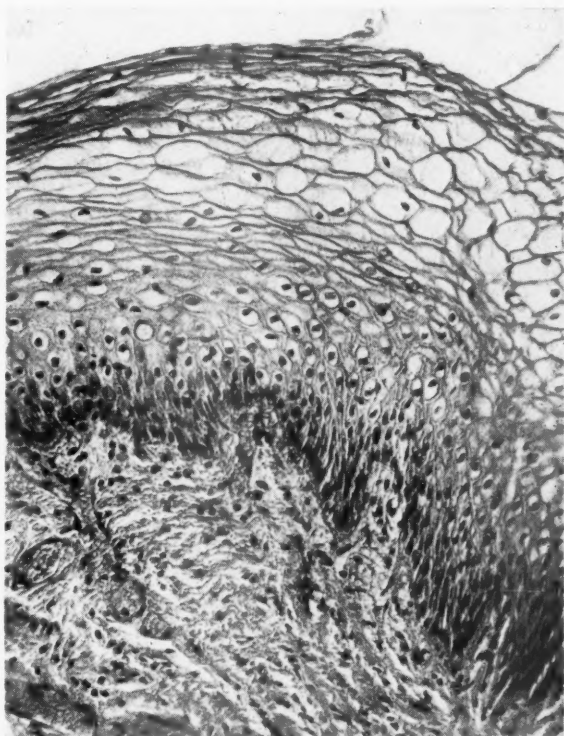


Fig. 2.—Vaginal mucosa at midcycle showing marked activity in the basal layer, pyknotic nuclei in the intermediate layer, and remnants of nuclei in the superficial cornified zone.

In a similar manner, the effect of estrogenic hormone in causing a deposition of glycogen in the vaginal epithelium of monkeys was demonstrated by Robertson, Maddux, and Allen.<sup>6</sup> Like observations were made by Krumm<sup>7</sup> in postclimacteric women and it has since been shown to also occur in children and oophorectomized women by other observers.

*Progesterone.*—The effects of progesterone on vaginal biology are difficult to evaluate. In physiologic dosages, progesterone itself appears to have little effect on the proliferation of the vaginal epithelium.<sup>8</sup> In

large dosages, progesterone will induce some degree of cornification in castrated rodents.<sup>9</sup>

Rakoff<sup>10</sup> has recently shown that, in large dosages (20 to 60 mg.), some degree of vaginal epithelial proliferation and cornification can be induced in castrate and postmenopausal women, although not nearly so marked as is obtained with estrogens.

When estrogen and progesterone are given simultaneously to the castrated rodent, progesterone appears to partially inhibit the estrogen effect.<sup>11</sup> If estrogen is given for a sufficient time to produce full cornification, and then progesterone is added, a similar inhibitory effect may be demonstrated while, if estrogen is added after progesterone, marked cornification is difficult to obtain. From a study of human vaginal smears, it would appear that the regressive changes which are noted during the luteal phase of the cycle are also probably due to the combined action of progesterone and estrogens.

*Androgens.*—In physiologic dosages, the androgens generally cause atrophic changes in the vaginal epithelium of human beings.<sup>12</sup> McCahey and Rakoff<sup>13</sup> showed that, in rats injected with relatively very large dosages of testosterone propionate, some degree of vaginal hyperplasia with some stratification and cornification could be induced. More recently, Clarke and Selye<sup>9</sup> have shown that various hormonally active steroids, whether folliculoids, luteoids, corticoids, or testoids, resulted in some vaginal epithelial growth in the rat when given in sufficient dosages. In the human being, Rakoff<sup>10</sup> found that, after submucosal injection of 25 mg. of testosterone propionate in the vagina of a castrate, some local vaginal hyperplasia resulted although, when given parenterally in dosages up to 300 mg. over a period of 4 to 6 weeks, similar results could not be obtained; indeed, in normal patients, such treatment resulted in atrophic changes.

*Cyclic Changes.*—The presence of cyclic changes in the human vaginal epithelium has been noted on histologic study by Stieve,<sup>14</sup> Dierks,<sup>1</sup> Puecioni,<sup>15</sup> Traut et al.,<sup>16</sup> and others. Although most workers agree that in the human vaginal mucosa during the sexually mature period of life there is a definite rhythm which it is possible to correlate with the ovarian cycle, it is quite obvious that these changes are not very marked and frequently are quite difficult to demonstrate. The reason for this appears to lie in the fact that the cyclic changes in the human vaginal mucosa are quite shallow and fail to go through the marked regression noted in the rodents. Apparently, throughout the menstrual cycle in the human being, there is always sufficient hormone to maintain the basic integrity of the epithelial layers.

In a series of 37 normal patients whom we have followed by weekly biopsies through several menstrual periods, there was very distinct evi-

dence of cyclic alterations. In many respects these were similar to the findings noted in the excellent studies of Davis and Hartman<sup>17</sup> in the rhesus monkey; however, as also noted by Traut and his associates,<sup>16</sup> in many instances these changes were not nearly so clear-cut in the human being, particularly those relating to the superficial and intermediate layers.

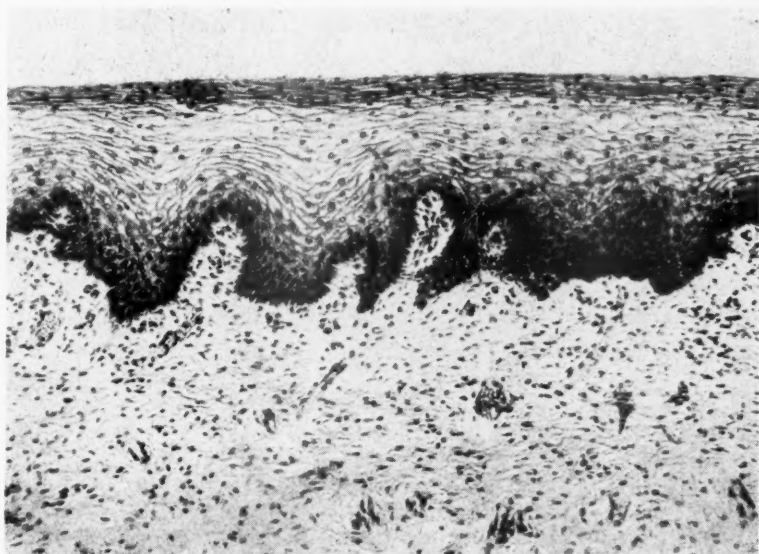


Fig. 3.—Vaginal mucosa, eighth day of the cycle, showing marked proliferation in the dark zone of the basal layer.

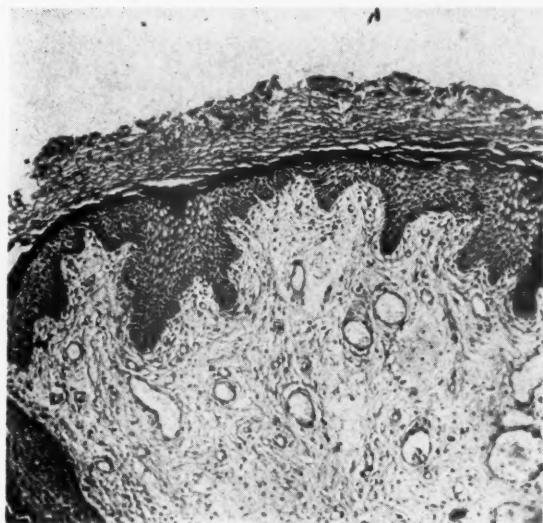


Fig. 4.—Vaginal mucosa, twenty-fifth day of the cycle (Best's carmine stain). Note the marked intraepithelial zone of cornification and the desquamation of the superficial layer.

Perhaps the most constant cyclic change noted in our biopsies was the proliferative changes evident in the dark zone of the basalis which in most of our cases was most marked between the seventh and fourteenth days and resulted in an increase in the thickness of the entire basal layer (Fig. 3). In the midcycle, the epithelium frequently attains its greatest thickness since growth and differentiation of the three layers have attained their maximum degree, and desquamation has not yet freely started. In the latter half of the cycle, the changes involve chiefly further cornification and desquamation of the superficial layer. In some instances a considerable thickness of highly cornified cells may remain until quite late in the cycle while, in other cases, whole plaques of cells may separate to the extent that only the basalis remains (Fig. 4). It is quite obvious that these regressive changes are difficult to follow by histologic methods while smear methods are admirably suited to this purpose. One feature of the premenstrual phase which is very often strikingly present in the biopsies is the increase of leucocytes in the sub-epithelial zone which may persist through the menstrual flow; not uncommonly, they may invade the epithelium proper as "wandering" cells and are best seen in the basalis.

In many respects it is far easier to follow these cyclic changes by cytologic studies of the superficial vaginal epithelium. Criteria for studying human smears were worked out by Dierks,<sup>18</sup> Smith,<sup>19</sup> and Papanicalaou.<sup>20</sup> More recently, simpler staining methods have been introduced by Shorr<sup>21</sup> and Papanicalaou,<sup>22</sup> and these have proved to be of considerable clinical usefulness. In the main, our findings in these patients do not materially differ from the excellent studies of Rubenstein<sup>23</sup> and will not be discussed in detail here. Suffice it to say that, as a rule, cyclic alterations could be more distinctly followed by the vaginal smear method than in biopsies and that as a means for orientation with regard to the ovarian cycle vaginal smears are unquestionably preferable. In the presence of inflammation or where interfering external factors have been present such as douches, vaginal smears are likely to be of little benefit whereas some useful information may be had from the biopsy.

## II. Glycogen

*Factors Influencing Deposition of Glycogen.*—During the sexually mature period of life the vaginal mucosa is very rich in glycogen, indeed, next to the liver it probably contains more glycogen than any other tissue of the body. As the vaginal epithelium grows under estrogen stimulation glycogen is deposited in the cells and can easily be demonstrated by special staining methods. This also occurs in the monkey<sup>6</sup> but not in lower animals such as the cow, sheep, pig, or rodents.<sup>8</sup> It has also been demonstrated that the glycogen content is scant or absent in those periods of life associated with low ovarian activity and is high during the reproductive period. It is present in greatest amount late



in pregnancy when the estrogen level is very high. Experimentally it has been shown to increase as cornification progresses.

Very few observations have been made concerning the effects of progesterone on the deposition of glycogen. Guest<sup>24</sup> states that in the castrated monkey, progesterone will not produce this response. Rakoff<sup>10</sup> has noted the deposition of some glycogen in castrate women after 20 mg. of progesterone, but smaller dosages were not effective.

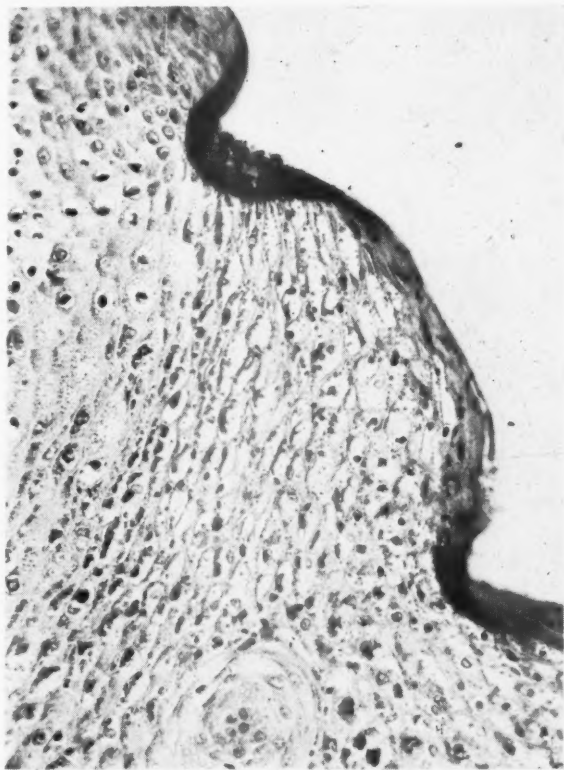


Fig. 5.—Vaginal mucosa (Best's carmine stain). High power magnification of the intermediate and superficial layers to show the granular character of the glycogen in the cells and the diffuse staining of the superficial zone of cornification.

In the human vaginal epithelium glycogen is absent or very scant in the basal layer of cells. The intermediate layer of cells, however, is very rich in glycogen, particularly those nearest the superficial layer. In these cells, glycogen is present in large granules which are easily seen when biopsies are stained by the iodine method, Best's carmine stain or the Feulgen method. In the superficial cornified layer glycogen is also abundantly present but because of the flattened state of the cells the staining is diffuse (Fig. 5). The glycogen in the superficial cells can be better demonstrated in smears than in biopsies. Glycogen per se appears to be present in the cells alone since ordinarily none can be demonstrated in the cell-free vaginal secretion.

The manner in which glycogen comes to be deposited in the vaginal epithelium is not known. In a vaginal biology symposium<sup>24</sup> the prevalent opinion appeared to be that there is a diffusion of glucose from capillaries and lymphatics into the basal layers, the cells of which take up the glucose and change it to glycogen. As the cells in the basal layer migrate toward the surface, glycogen becomes more abundant in the intermediate and superficial layers. It is postulated that this property of the conversion of glucose to glycogen is a specialized function of the vaginal epithelium since it does not occur in other similar epithelial structures such as the mucosa of the esophagus.

From chemical studies of the vaginas of monkeys Van Dyke and Ch'en<sup>25</sup> found that the concentration of glycogen was highest in the upper part of the vagina ranging from 2.36 to 2.98 per cent; in the midvagina it ranged from 1.93 to 2.48 per cent while in the lowest part of the vagina it was 0.64 per cent. They also demonstrated that after ovariectomy the concentration in the midvagina fell to less than 1 per cent but after injection of estrogens increased to as high as 4.42 per cent. Similar conclusions were reached by Krumm<sup>7</sup> by the rather approximate method of directly applying iodine to the vaginal wall (Schiller test) and noting that the portio vaginalis and fornices take the deepest stain while the mucosa of the lower half of the vagina takes very little stain.

Rakoff<sup>10</sup> made glycogen determinations on strips of vaginal mucosa obtained from two normal young women at operation. The strips were taken from the anterior or posterior fornix, middle third of the vagina and lower third of the vagina. The epithelium was stripped away from the mucosa so that on section it consisted almost entirely of epithelium and lamina. The tissue was dropped at once into absolute alcohol and glycogen determined after conversion to glucose. In the vaginal fornices glycogen ranged from 2.5 to 3.0 mg. per cent, in the middle third from 1.5 to 1.8 mg. per cent and in the lower third of the vagina from 0.6 to 0.9 mg. per cent.

Some valuable studies on the lability of the vaginal glycogen have also been made by Van Dyke and Ch'en. They showed that following starvation the glycogen of the vaginal mucosa in the monkey is not appreciably reduced although, as is well known, the concentration of hepatic glycogen was markedly lowered. Similarly, the concentration of vaginal mucosa glycogen was not affected by large doses of thyroxin, whereas there was a marked reduction in hepatic glycogen. They concluded therefore, that the only method for reducing the concentration of glycogen in the vaginal mucosa so far discovered is that of bilateral ovariectomy. From more recent studies it seems that the same effect may be accomplished by the administration of androgens.<sup>26</sup> The underlying mechanism of course may be similar, namely, an interference of the estrogen effect on the vaginal mucosa.

*Factors Influencing the Utilization of Glycogen.*—It has long been assumed that the glycogen of the vaginal mucosa is converted into simpler carbohydrates and then into lactic acid and is thus the primary source of the vaginal acidity in the human being. Much difference of opinion exists, however, as to just how this is accomplished. The possibilities which have been suggested are the following:

(1) *Glycogen is attacked directly by certain bacteria (particularly the lactobacillus of Döderlein) and converted into lactic acid.* This was the hypothesis favored by Zweifel<sup>27</sup> and later supported by Schultheiss<sup>28</sup> who claimed that under suitable conditions Döderlein's bacillus can directly attack and break down glycogen with the production of lactic acid: this could not be supported by the work of Smordinzew and Kott<sup>29</sup> but was confirmed by the in vitro experiments of Cruickshank<sup>30</sup> in which he demonstrated that Döderlein's bacillus and it alone, of the organisms likely to be present in the vagina as saprophytes or pathogens, is capable of directly fermenting glycogen with the production of acid.

(2) *Glycogen is partly fermented to simpler carbohydrates by enzymes present in the vagina; these are then further reduced by Döderlein's bacillus.* A number of workers have assumed that glycogen must first be converted to simpler sugars before it can be utilized by Döderlein's bacillus. This theory would explain the observation<sup>3</sup> that although the vaginal secretion was moderately acid shortly after birth, the acidity becomes further increased after 3 or 4 days when Döderlein's bacilli appear. Guest<sup>24</sup> has also made some observations indicating that in the vaginal wall there is a certain amount of carbohydrate of a lower molecular weight than glycogen, which does not stain with iodine or Best's carmine. He also believes that the material that does stain may not be free glycogen entirely since glycoproteins may also be stained by these methods.

(3) *Bacteria other than Döderlein's bacilli are capable of further fermenting the carbohydrates resulting from enzymatic breakdown of glycogen.* This viewpoint has been favored particularly by Weinstein and his associates<sup>31-32</sup> on the basis that in observations on monkeys and postclimacteric women treated with estrogens, there appeared to be very little correlation between the degree of acidity of the vaginal mucosa and the number of Döderlein's bacilli which can be demonstrated by cultures. This conclusion is not in accord with the majority of clinical studies. From their data the above workers suggest that the glycogen is broken down to simpler sugars by some enzymatic action and these monosaccharides are attacked by other bacteria such as *E. coli*, *B. aerogenes*, staphylococci, and streptococci. The resulting acid is inimical to these organisms and by killing them allows the Döderlein's bacillus to become the predominant type.<sup>31, 33</sup>

(4) *Glycogen is converted to lactic acid by enzymatic action alone.* This theory has been supported by the observation that in newborn

children the vaginal secretion is distinctly acid, usually, pH 5.0 to 5.8 even before bacterial implantation occurs, and that lactic acid is already present at that time. Blair-Bell<sup>34</sup> also found lactic acid in hematocolpos fluid which was sterile. Although Cruickshank<sup>30</sup> was unable to demonstrate a nonbacterial enzyme in vaginal secretion, he admitted that in

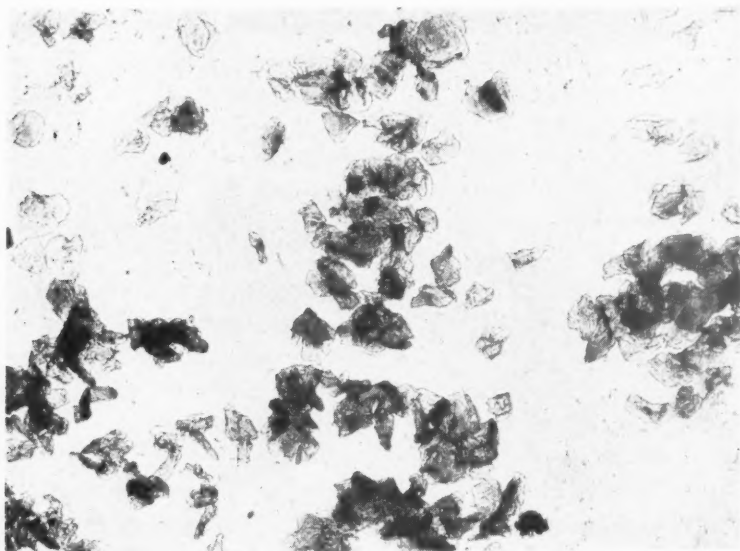


Fig. 6.—Vaginal smear glycogen stain showing moderately heavy concentration of glycogen in most of the epithelial cells (+3).

view of the presence of glycogenase in fresh serum the glycogen in the vaginal cells may be converted in the absence of bacteria by such an enzyme to glucose from which, in turn, lactic acid is produced by a glycolytic cellular enzyme. A number of other workers<sup>35</sup> have also been unable to demonstrate enzymatic activity in cell-free vaginal fluid, but have intimated that such enzymes may have been destroyed by the technical procedures involved.

*Observations of Glycogen in the Vaginal Epithelium.*—In our studies the glycogen content of the vaginal epithelium was determined from vaginal smears and biopsies prepared with glycogen stains.

The smears were taken from the lateral wall of the exposed vagina with a cotton-tipped applicator. The smear was permitted to dry and then treated as follows: it was fixed in absolute alcohol, and then allowed to dry, after which it was stained with Lugol's iodine solution for 3 minutes and again dried; the excess iodine was then removed by washing with 95 per cent alcohol. When the smear dried it was examined microscopically. Glycogen is indicated by a diffuse red-brown stain of the epithelial cells, the intensity of which depends on the amount of glycogen present. This may be indicated by grading the smears by

comparison with standards from 0 to plus 4 (Fig. 6). If desired, the staining of the glycogen granules may be made more permanent by treating with a dilute solution of  $\text{HgSO}_4$  after staining with Lugol's solution, as suggested by Mancini and Celani-Barry.<sup>36</sup> The glycogen granules retain a deposit of  $\text{HgI}_2$ . Another satisfactory method<sup>37</sup> is to add Lugol's solution directly to a suspension of fresh vaginal secretion and to examine it in the wet state. Mack<sup>38</sup> has suggested exposing the slide to the vapors of Lugol's solution as a staining method. It is, of course, appreciated that these methods indicate only the amount of glycogen in the *superficial* vaginal epithelium and that they are only roughly quantitative. For most clinical purposes, however, these methods appear to be very satisfactory, and have even been suggested as an objective guide to estrogen therapy.<sup>39</sup>

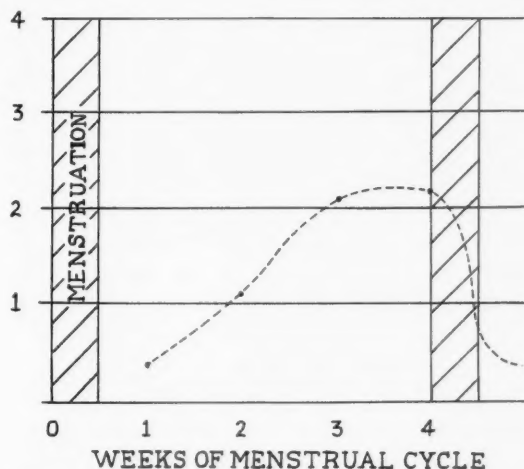


Fig. 7.—Average glycogen readings of 372 iodine-stained smears from 37 women taken at various phases through one to three menstrual cycles.

- 0 = None demonstrable
- 1 = Distinct traces
- 2 = Moderate staining
- 3 = Deep staining
- 4 = Intense staining

From the study of 372 smears from 37 women prepared at frequent intervals throughout the cycle (Fig. 7) it is apparent that an increase in the intensity of the glycogen stain is generally noted at about the time of midcycle. This generally increases further until a peak is reached in the last week of the cycle; a few days before the onset of menstruation a very distinct fall in glycogen concentration is commonly noted. This fall generally occurs at about the time when the disintegrative changes in the vaginal cells characteristic of the late premenstrual phase are noted. It will be noted that the smoothed curve of our observations on the cyclic variations in glycogen content in these 37 cases roughly corresponds to the curve for estrogen excretion.



In our studies the glycogen content of the whole vaginal epithelium was determined from punch biopsies. These were fixed in absolute alcohol or a fixative consisting of 9 parts of absolute ethyl alcohol to 1 part of 40 per cent formaldehyde neutralized with  $\text{MgCO}_3$ . We have tried several of the methods commonly employed<sup>40</sup> including the Best's carmine, iodine and Bauer-Feulgen methods, but for general use we prefer Best's carmine stain.

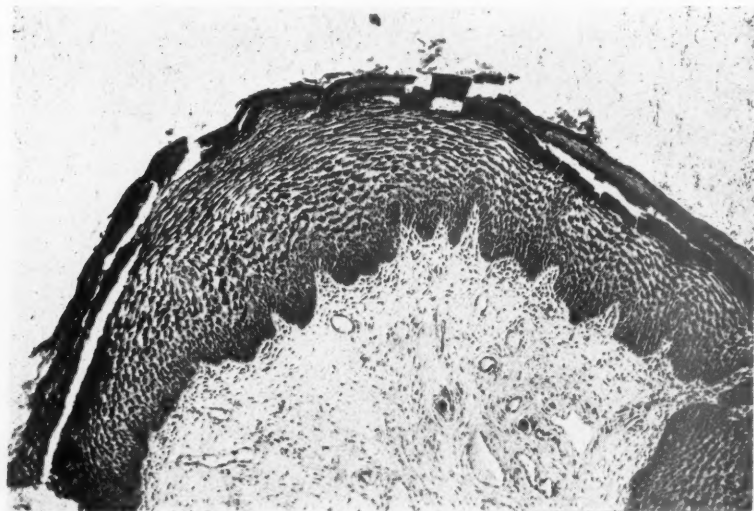


Fig. 8.—Vaginal mucosa (Best's carmine stain) tenth day of the cycle, showing heavy concentration of glycogen in all layers except the dark zone of the basalis.

It is quite obvious that the glycogen-stained biopsies afford information quite different from glycogen-stained smears. The former are an indicator of the glycogen content throughout the thickness of the epithelial layer and afford information concerning the distribution of glycogen in the various layers, and some indication of its physical nature within the cells proper. On the other hand, biopsies are not as easily prepared nor can they be taken so frequently as can smears; furthermore, in the normal vagina the concentration of glycogen in the superficial epithelium as shown by the smear method appears to be a much better indicator of cyclic alterations than can be obtained from the biopsies.

Examination of a typical vaginal biopsy stained by the Best-carmin method (Fig. 8) reveals that glycogen is usually absent from the basal layer of cells, although occasionally, particularly in biopsies taken during the luteal phase, discrete granules of glycogen taking the beautiful metallic carmine stain, may be noted in the rapidly dividing basal cells. The amount of glycogen gradually increases as one approaches the middle zone of the intermediate layer and then becomes quite heavy until the superficial layer is reached. Here the concentration of glycogen is also high, but very often is present in a diffusible form which uniformly

stains the entire cell. The glycogen, however, appears to be contained entirely within the cells proper since none of the stained material is noted in the intracellular spaces. From a study of these specimens one obtains the impression that the glycogen, as such, is formed primarily in the intermediate layer of cells and is converted into a more easily utilizable form in the keratinized cells of the superficial layer.

*Glucose.*—The presence of reducing substances, probably glucose, in the vaginal secretion has long been known, although as already indicated there is much disagreement concerning its origin. The quantity present is reported to vary from zero up to 4 per cent of the fluid. At present it has not been possible to correlate the concentration of glucose with either the pH, the phases of the menstrual cycle, or the amount of lactic acid present.<sup>41</sup> This is not surprising, however, in view of the fact that glucose is probably an intermediary product which is undergoing rapid alteration. It has been suggested that the glucose thus formed may serve as a source of energy for the spermatozoa. On the other hand, MacLeod<sup>42</sup> points out that glycogen can be used directly by the sperm since it possesses an enzyme which can break it down.

### III. Vaginal Acidity

Zweifel, who demonstrated in 1877<sup>43</sup> that the vaginal discharge is usually acid, also determined that the acidity was due to lactic acid and showed later<sup>27</sup> that it was present as racemic lactic acid both in free and bound form. It has since been generally accepted that the acidity of the vaginal secretion is due in most part, if not entirely, to lactic acid, the concentration of which may reach as high as 2 to 3 per cent.<sup>24</sup> The possibility that other acids may also be present was suggested by von Jasche<sup>41</sup> since he did not find any correlation between the glycogen of the vaginal epithelium and the lactic acid content. It is now generally agreed, however, that, provided there is no infection or other abnormality present, high degrees of vaginal acidity are generally associated with an abundance of glycogen, whereas the acidity is markedly reduced when the glycogen is scant or absent due to hypo-estrogenism. It has not yet been possible to demonstrate a strictly quantitative relationship of the glycogen content and the vaginal acidity through the cycle. Indeed, it would be rather surprising if such a relationship exists since the opposing factors of glycogen deposition and glycogen utilization are occurring simultaneously; also very little attention has been given to the possibility that the acidity of the vagina may be, in part, the result of factors other than the fermentation of glycogen. Although it is well recognized that the acidity is greatest in those life phases in which glycogen is present, the fact remains that in childhood and in the postmenopausal period, acid reactions of pH 5.5 to 6.5 are not uncommon. Furthermore, it has been shown by Beilly<sup>44</sup> that in the rat, a species in which glycogen is entirely absent from the vaginal mucosa, the pH undergoes a marked cyclic variation and during estrus falls to

about 4.5 while during the diestrus stage, the readings may approach a pH of 7.0. No explanation of the mechanism of these pH changes is offered except that they are apparently dependent in some way upon estrogenic hormone.

Even in the early studies on vaginal biology there was considerable interest displayed in the degree of vaginal acidity since it had been demonstrated that in various abnormal conditions this became reduced, and it was believed that a normal degree of acidity served as a protective mechanism in preventing the growth of various pathogenic organisms in the genital tract. Since then, many observers have pointed out that there is a distinct correlation between the degree of vaginal acidity and the type of vaginal flora; the acidity being highest in vaginal secretion containing Döderlein's bacilli alone (Grade I) and lowest where Döderlein's bacilli are absent (Grade III).

Further interest in making accurate determinations of the vaginal pH was stimulated by the possibility that distinct changes could be demonstrated in correlation with the ovarian cycle. In fact, from the experience which has thus far accumulated there is good reason to believe that such is the case, although there are often many factors in the patient which tend to obscure this correlation, and certain technical difficulties which may interfere with the accuracy of the determinations. Among these factors are the following: (1) the amount of secretion available in normal cases is often very scant and occasionally no free discharge at all can be recovered; (2) the discharge may be contaminated with cervical secretion; (3) any type of mechanical manipulation such as digital examination or coitus will lower the vaginal acidity; (4) the vaginal pH will also be altered if vaginal douches and other intravaginal medication are employed within 24 hours preceding the determination; (5) if there is any type of inflammatory lesion present the vaginal acidity will also be lowered; (6) even the presence of nonpathogenic bacteria of various kinds will change the vaginal pH. It is therefore apparent that the results obtained will not be a true indicator of the normal biochemical mechanism if any of these interfering factors are present.

*pH in Various Phases of Life.*—From the data now available it is quite apparent that the pH range varies in different life phases in association with estrogenic function. In studies conducted on a group of newborn infants Cruickshank and Sharman<sup>3</sup> obtained the following results:

AGE	RANGE	AVERAGE
First 24 hours	5.3 to 6.4	5.7
Second day	4.6 to 6.4	5.6
Third day	4.7 to 6.8	4.9
Fourth day	4.7 to 5.6	4.8
Ninth day		4.9
	Approximately	
Three to four weeks	5.0 to 7.0	
Six to eight weeks	5.0 to 8.0	

They concluded that from birth until the ninth day the reaction of the secretion was acid, being highly acid from the third to the ninth day, whereas at 3 to 6 weeks it was generally near neutrality. During the remainder of childhood and until puberty is approached, the vaginal secretion remains nearly neutral, generally being slightly alkaline. The pH in children from 2 to 8 years usually falls in the range from pH of 6.0 to 8.0. Near puberty the vaginal secretion becomes distinctly acid and after the menstrual function is established the pH soon falls within the range of 4.0 to 5.0 in normal cases. This is approximately the range of the vaginal acidity which continues throughout the reproductive period until the menopause is approached.

During pregnancy there is a distinct tendency for the vaginal secretion to reach its maximum acidity; especially during the latter months when the estrogen level reaches its peak. The pH values during this period tend to approach pH 4.0 and occasionally reach as low as 3.8.

With the decrease in ovarian activity which occurs in the premenopausal phase there occurs a diminution in vaginal acidity. After the cessation of the menses the values tend to approach neutrality and not infrequently become alkaline, rarely, however, being more than pH 7.8.

*pH Changes in Association With the Menstrual Cycle.*—Rhythmic variations in vaginal acidity in association with the ovarian cycle have long been suggested but actually very few reliable data are available, probably because the range of variation throughout the cycle is small and the technical difficulties are great. As early as 1918 Gräfenberg<sup>45</sup> claimed to have demonstrated such rhythmic variations and stated that the acidity of the vagina diminishes from the early part of the cycle to the middle of the intermenstrual period when there is an interval of reduced acidity related to the rupture of the follicle. The acidity then rises to its highest level shortly before the next period. In their review of the subject, Oberst and Plass<sup>46</sup> point out that Heinlein<sup>47</sup> using the same technique was unable to detect regular cyclic changes in acidity but did note slight variations from day to day. Oberst and Plass<sup>46</sup> present some interesting data on cyclic variations in vaginal acidity in normal nonpregnant women and also in nonpregnant women with pathologic discharges based on pH readings of the vaginal discharge and also on total acidity obtained from titration values. Their data indicate that during the intermenstrual period the pH ranges from 4.0 to 4.5 but approaches or exceeds neutrality during the early days of menstrual bleeding; apparently, they were not able to note any significant variations in association with ovulation or other ovarian phases. Zuck and Duncan<sup>48</sup> on the other hand, obtained pH values of vaginal secretions which show not only a rhythmic variation with the menstrual cycle but also a characteristic rise at the time of ovulation. These data are not in apparent agreement with those of Rakoff<sup>10</sup> or of Guest<sup>24</sup> who find that the lowest values in normally menstruating women are obtained

during the ovulatory phase. It is to be pointed out, however, that the observations of Zuck and Duncan were made on mixed vaginal secretion and were no doubt influenced by the increase in alkaline cervical discharge which occurs at the time of ovulation. Our determinations were made directly on the vaginal mucosa, taking care to exclude contamination with cervical discharge.

*Vaginal pH as an Indicator of Ovarian Activity.*—It has already been pointed out that there is a marked difference in vaginal pH in different life phases due to variations in the ovarian function. Similarly, it has since been pointed out by a number of workers<sup>49, 50</sup> that pH determinations are also a useful indicator of diminished ovarian function and that these may also serve as one objective guide in treatment with estrogens. Only rarely are pH determinations of value in determining states of hyperestrogenism, since even with excessive concentrations of the hormone the readings do not usually fall below pH 4.0. Occasionally in pregnancy, values as low as 3.8 are encountered. In young women with so-called "hyperhormonal" leucorrhea, corresponding values have been encountered.

*Correlation of Vaginal pH and Vaginal Flora.*—Numerous observers have pointed out the relationship which exists between vaginal acidity and the type of vaginal flora, based upon the plan of recognizing three grades of bacterial flora: Grade I consisting of a homogeneous bacterial flora of Döderlein's bacilli; Grade II, Döderlein's bacilli plus other organisms; Grade III, organisms other than Döderlein's bacilli. Thus, Cruickshank and Sharman<sup>3</sup> make the following correlation:

GRADE	pH
I	4.0 to 4.4
II	4.6 to 5.6
III	5.6 to 7.6

Most workers feel that the range is not nearly so demarcated and that there is often considerable overlapping. Thus, on observations made by direct glass electrode readings of the middle vagina, Trussell and MacDougal<sup>51</sup> found the following values in late pregnancy:

GRADE	RANGE	AVERAGE
I	3.96 to 5.72	4.58
II	3.99 to 6.10	5.03
III	4.92 to 6.88	5.69

We have obtained strikingly similar results in a large group of non-pregnant patients (Table I).

A rather new note on this subject has been introduced by Weinstein and Howard<sup>55</sup> who question whether such a correlation exists at all. Their work is based upon studies made on menopausal women following injections with estrogenic hormone. They noted the usual fall in pH but could find no definite correlation between the degree of acidity of the vaginal secretions and the presence or absence of the Döderlein's



bacillus. Their findings support the clinical observations that low pH values are sometimes encountered even in the absence of Döderlein's bacilli, but this fails to alter the fact that in most *normal* women, normal pH values are commonly associated with a Grade I flora.

TABLE I. CORRELATION OF VAGINAL FLORA AND pH

	pH:	3.9 TO 4.5	4.6 TO 5.0	5.1 TO 5.5	5.6 TO 6.0	6.1 TO 6.5	6.6 TO 7.0	7.1 TO 8.0	8.1 TO 9.0	AVER- AGE
Grade I (210 patients)	%	52.4	34.3	9.5	3.8					4.56
Grade II (187 patients)	%	19.8	32.1	29.9	10.7	6.4	1.1			5.09
Grade III (323 patients)	%	9.3	17.4	33.1	24.1	9.3	5.3	0.6	0.9	5.54

### Observations on Vaginal pH

*Method.*—Until recently most determinations on vaginal acidity were made by one of the following methods: (1) collecting vaginal secretion and then determining the acidity by titration methods against various indicators; (2) by determining the concentration of lactic acid; (3) by measuring the pH of the fresh or diluted secretion; (4) indicator papers also have been employed for the rather rough measurement of vaginal pH. These methods have obvious disadvantages. It is often difficult to know from what part of the vagina the secretion originated and how much admixture there has been with cervical discharge; not infrequently, it is difficult to obtain a sufficient amount of material to make a reliable determination; some of the methods require dilution of the discharge which may also make an appreciable difference; also there is the possibility that the pH may change outside of the vagina as a result of evaporation, loss of CO<sub>2</sub>, and so forth. Trussell and MacDougal<sup>51</sup> made the suggestion that the pH of the vaginal mucosa itself could be determined by exposing the vagina and directly introducing the electrodes of a potentiometer. Trussell and MacDougal employed a glass electrode plus a capillary tube connecting with a calomel electrode. The advantages of this method are at once apparent. The pH may be obtained with a high degree of accuracy at any particular point in the vagina desired. The readings are obtained rapidly and conveniently and may be checked as frequently as is necessary. All of the technical difficulties of dealing with the secretion itself are avoided.

We have modified the electrode used by Trussell and MacDougal as shown in the accompanying figure (Fig. 9). The glass electrode has been made thinner and longer than the usual large electrode and the end has been curved to make it convenient to touch various portions of the vaginal wall. The calomel electrode is suspended in a container filled with a saturated solution of KCl. This is connected by rubber tubing with a thin, hard glass pipette bent to approximate the length and shape of the glass electrode so that it can be fitted snugly next to it with rubber

bands or a special holder. In this manner the two electrodes can then be introduced easily into the exposed vagina. Prior to its use a small amount of KCl solution is flushed through the tubing and a drop is permitted to collect at the point at which contact is made with the vagina. It is important to place the glass electrode at the exact point at which the reading is desired. Contact with the calomel electrode can be made at any neighboring point. In our setup the electrodes lead to a Beckman pH meter. When firm contact with the vaginal mucosa is

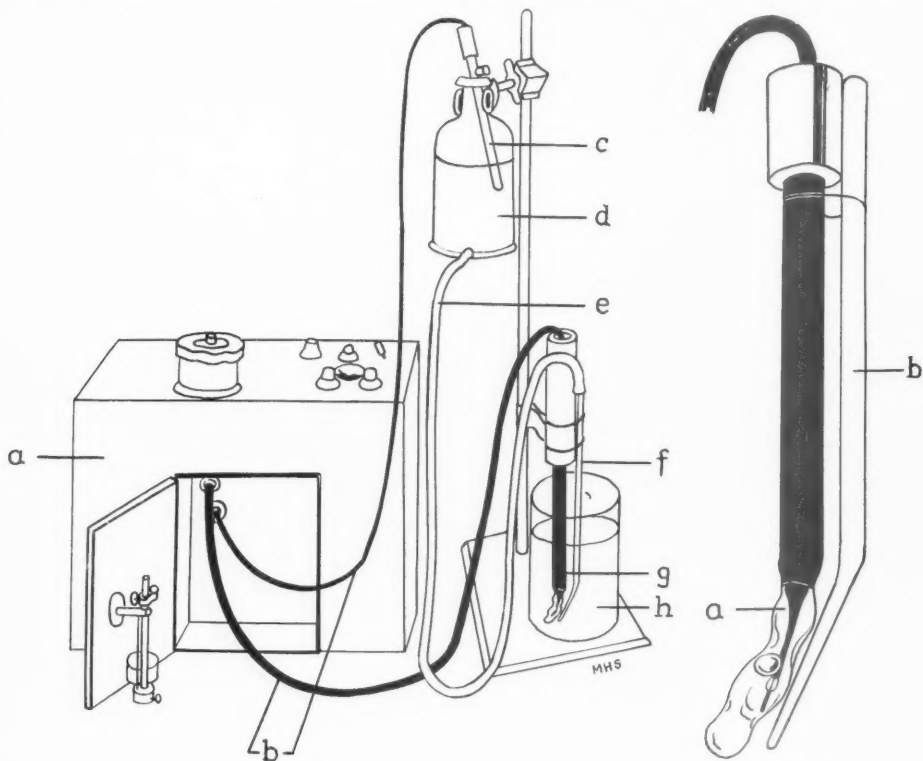


Fig. 9A.

Fig. 9B.

Fig. 9A.—Shows setup employed in taking vaginal pH. (a) Beckman pH Meter, (b) leads to electrodes, (c) calomel electrode, (d) saturated solution of potassium chloride, (e) rubber tubing, (f) thick-walled glass tubing bent to fit snugly against glass electrode, (g) special glass electrode, (h) solution of bichloride of mercury 1:5,000 in which electrodes rest when not in use.

Fig. 9B.—Close-up of the vaginal electrodes (a) glass electrode made especially thin and curved for intravaginal use [length  $6\frac{1}{4}$  inches, thickness  $\frac{3}{8}$  inch], (b) thick-walled glass tubing bent to fit snugly against glass electrode; serves as an extension of the calomel electrode.

established the pH corrected for temperature may be obtained directly in a few seconds. After they have been used, the electrodes are carefully wiped in a solution of bichloride of mercury 1:5,000 and are permitted to rest in a beaker containing this solution until needed again.

As a routine, we have found it convenient to make readings of the vagina in the middle third of one of the lateral walls, in the anterior fornix, in the posterior fornix, and at the cervical os. For the latter

determination it is essential that the glass electrode fit directly into the os since otherwise the highest reading may not be obtained.

*pH Gradient of the Vagina.*—The highest pH readings (lowest acidity) are generally encountered in the lower third of the vagina (Fig. 10). The pH in the middle third of the vagina is considerably

### PH Gradient of the Normal Lower Genital Tract

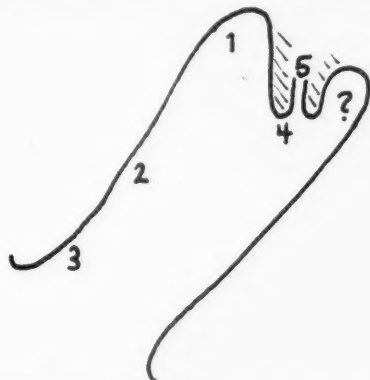


Fig. 10.—Highest readings are generally obtained in the anterior fornix (1); intermediate readings (usually the most constant) in the middle third of the vagina; (2) and lowest readings near the vaginal orifice. (3) The readings in the posterior fornix are rather inconstant because of the presence of cervical discharge. Higher pH readings are obtained at the cervical orifice; (4) and these may approach or exceed neutrality within the cervical canal. (5) The special vaginal electrodes may be obtained from Arthur H. Thomas & Co., Philadelphia, Pa.

### Average Mid-Vaginal pH in 37 Normally Menstruating Women

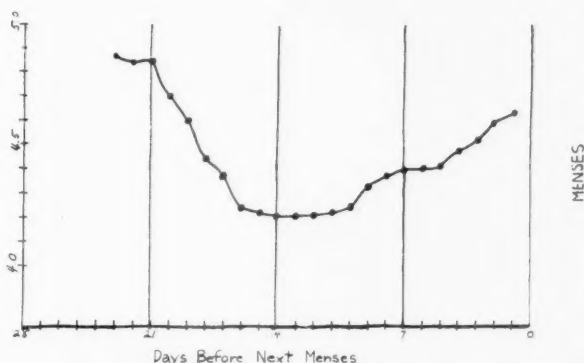


Fig. 11.—Average pH readings in 632 readings made on 37 normally menstruating patients.

lower and usually the most constant and, as a rule, gives values quite similar to those obtained from mixed vaginal secretion. In our experience, the lowest pH values are obtained in the anterior fornix. The readings in the posterior fornix are strongly influenced by the amount of cervical discharge which has collected here; if but little of this is

present the pH of the posterior fornix may be almost identical with that of the anterior fornix, but more often because some contamination with cervical discharge has occurred, it approaches that of the mid-vagina. In those instances in which a profuse cervical discharge is present, the acidity is usually markedly reduced.

*Cyclic Variations of pH in Normal Women.*—We have collected a total of 632 readings of the midvaginal pH at various periods of the menstrual cycle on 100 women in whom all other vaginal factors were normal (Fig. 11). In all determinations save 19 instances (3 per cent), the range of the pH varied between 4.0 and 5.0. In 2 recordings a pH of 3.9 was obtained, while in 17 other instances the range was found to be 5.1 to 5.6. (In a number of the latter cases we have reason to believe that the higher pH values may have been influenced by recent coitus or douching.) Based on these findings, it would appear that for all practical purposes the normal pH range of the midvagina throughout the cycle lies between 4.0 and 5.0. It is to be pointed out that these values do not include readings taken during menstruation since during this phase considerably higher pH readings may be obtained because of contamination with the alkaline blood. We have found, however, that if the blood is carefully wiped away, the readings are quite commonly in the neighborhood of pH 5.0.

In 37 cases in which we have obtained a sufficient number of readings during several cycles, there is evidence of a periodic variation of pH (Fig. 11). If average determinations are made based on the number of days before the next menses, it will be noted that the pH is highest in the early days of the cycle and that it gradually falls to reach the lowest values in the midcycle. This high degree of acidity is maintained through most of the luteal phase but gradually tends to rise in the premenstrual phase.

In a number of patients, we made daily pH determinations during the intermenstrual period along with vaginal smears and basal rectal temperatures in order to determine whether there was any sharp variation in association with the ovulatory type of smear. Except for the gradual decline noted, we were not able to determine any significant sharp change in midvaginal pH. In several instances, however, there was a very decided increase in the pH at the cervical os. This may be related to the increase of the cervical discharge which has been associated with ovulation.<sup>52</sup>

The readings in some of the cases studied were quite erratic and it was not possible to demonstrate any significant fall at the midcycle. This may be attributed to certain factors:

1. It is well known that some normally menstruating women may have irregular excretion of the gonadal hormones. These may be the patients in whom the most irregular values were obtained.

2. In some of the patients anovulatory cycles may have been present. In this respect it might be pointed out that in a few of the cases studied, the midvaginal pH remained quite constant from day to day.
3. It is acknowledged that an insufficient number of readings may have been made during each cycle, and therefore, transitory changes may not have been detected.

#### IV. Vaginal Flora

It is well recognized that the biochemical factors present in the vagina are capable of determining to a considerable extent the character of its bacterial flora. Thus, the organisms within the vagina are considerably different from those found on the vulva and frequently different from those found in the cervix proper. Moreover, the vaginal flora changes in the various life phases just as do the other biologic factors which have been discussed.

*Vaginal Flora in Various Periods of Life.*—At birth the vagina is sterile. Organisms make their appearance in 12 to 24 hours<sup>3</sup> and at first consist of a small number of such organisms as staphylococci, enterococci, and diphtheroids. But as early as the second or third day, these are commonly replaced by a practically pure culture of lactobacilli (Döderlein's bacilli<sup>4</sup>). It is supposed by some that the latter organisms originate by contamination from the feces as soon as the lactobacilli become established in the intestinal tract of the newborn; but this is a mooted question. The important factor is that within a few days, a distinctive bacterial flora becomes established in the vaginal tract of the infant and is maintained so long as the biochemical factors remain under the influence of the estrogens, derived from the maternal circulation. Within a week or ten days when the latter has been completely excreted, Döderlein's bacilli are in turn replaced by a varied flora of staphylococci, nonhemolytic streptococci and coliform and diphtheroid bacilli. This is a striking clinical experiment illustrating the influence of estrogens in determining the vaginal flora. The mixed bacterial flora persists until puberty. Shortly before or soon after the menarche, Döderlein's bacillus reappears, and as the ovarian function becomes well established, it tends to become the predominant organism in the vaginal tract. During the period of sexual maturity the vaginal flora may consist of Döderlein's bacilli alone, or may be associated with the organisms already mentioned as well as with anaerobic streptococci which appear to be commonly present in the female genital tract.<sup>53</sup> Under unfavorable circumstances Döderlein's bacilli may disappear completely and be replaced by some other organism, but more commonly by a variety of bacteria, usually saprophytes, but occasionally pathogens may also be present. This concept is the basis for the simple classification of Schröder.<sup>54</sup>



- Grade I: Consists of Döderlein's bacilli only.  
Grade II: Consists of Döderlein's bacilli and other organisms.  
Grade III: Consists of organisms other than Döderlein's bacilli.

This classification of flora has long been accepted also as an index of the normality or state of cleanliness (Reinheitsgrade) of the vagina in which the Grade I flora is accepted as normal and the Grade III as the most abnormal.

During pregnancy when the maternal organism is surfeited with estrogens, conditions appear to be particularly favorable for the lactobacilli and it has been shown by many studies that as pregnancy progresses the proportion of patients with a Grade I flora increases. Following parturition and for a varying length of time during the puerperium, the vaginal flora resembles that of the vulva, not merely because of the rapid decline in estrogenic hormone, but also because of the inhibiting influence of the alkaline lochia and the trauma incident to labor.

In the years of diminished ovarian function which come with the menopause and thereafter, the vaginal flora gradually reverts to the childhood type, although it cannot be denied that a small proportion of postmenopausal women may harbor Döderlein's bacilli for many years, just as many postmenopausal women retain some minimal ovarian function for many years.

*What Is the Normal Vaginal Flora?*—It has already been intimated that the character of the vaginal flora is determined largely by the underlying mechanism upon which the physiologic factors in the vagina are based; namely, ovarian activity, glycogen deposition and pH. Since, under normal circumstances, glycogen content and acidity are influenced by the degree of ovarian function, it is reasonable to expect the vaginal flora to vary with the various life phases associated with changes in ovarian function. As has already been pointed out, through most of childhood and in the postmenopausal period when there is but little ovarian function the vaginal flora is varied, whereas during the sexually mature period of life a homogeneous flora of lactobacilli tends to become established. On the other hand, it cannot be denied that there are a small percentage of clinically normal cases in which the various physiologic characteristics also appear to be within the normal range and yet organisms other than Döderlein's bacilli are present. Also, the converse is not infrequently true; mainly, that patients with evidences of decreased ovarian function and decreased acidity may harbor the lactobacilli. This is graphically illustrated in Table I in which the mid-vaginal pH of patients is plotted against the grade of flora.

From these observations it is apparent that although the presence of a Grade I flora may be a good indicator that the vagina is clinically normal, it does not necessarily mean that it is physiologically normal, although there is a strong probability that it is.

From the data which are available, it appears that inhabitation of the vagina by the lactobacilli is dependent mainly, if not entirely, upon the degree of acidity. Apparently, there are but few organisms which, having an opportunity to enter the normal vagina, can survive and flourish in an environment of pH 4.0 to 4.5. Not infrequently, certain yeasts may do this; certain yeast-like fungi also appear to be favored by such an environment, but the latter cannot be considered normal since they often produce an inflammatory lesion of the vagina and vulva. Next to these, certain aciduric streptococci (*Streptococcus fecalis*) and certain strains of diphtheroids are able to tolerate moderate degrees of acidity.

For purposes of definition and also in the selection of patients with normal vaginas for study, it is our belief that the normal vaginal tract is one in which not only the histologic and biologic characteristics are within normal but in which a homogeneous flora of lactobacilli are present.

*Döderlein's bacillus.*—The first comprehensive description of this organism appeared in a classic monograph of Döderlein on the vaginal flora. Since then, numerous observations but very few extensive studies concerning this organism have been made. Our present knowledge of this organism may be summarized as follows:

*Morphologic Characteristics.*—As seen in vaginal smears, Döderlein's bacillus most commonly appears as a rather long gram-positive rod of moderate thickness, often slightly curved with ends which tend to be rounded. This organism, however, is capable of considerable pleomorphism and a number of subspecies have been described based on morphologic variations.<sup>41</sup> The more common morphologic variants are: (1) a short, thick, blunt rod usually appearing singly; (2) an elongated, thin rod 2 to 3 times the length of the usual form and often distinctly wavy in appearance; (3) a very short rod, almost a coccobacillus which very frequently appears in diploid formation and can easily be mistaken for diphtheroids or enterococci.

*Cultural Characteristics.*—From its general cultural characteristics this organism has been classified as a member of the lactobacilli. The organism is rather fastidious in its cultural requirements and does not grow well on ordinary media. Among the special media most suitable for its growth are whey-agar, tomato juice agar or broth, and particularly the tomato-milk medium of Weinstein et al.<sup>55</sup>

The colony and cultural characteristics of Döderlein's bacillus and *Lactobacillus acidophilus* have been shown to be very similar<sup>56</sup> so that differentiation cannot be made on these grounds. It was shown by these same workers that Döderlein's bacillus is serologically different from *L. acidophilus* and in fact, several strains of Döderlein's bacilli differed from each other serologically.

*Other Organisms Found in the Normal Vagina.*—It is well recognized that the apparently normal vagina may harbor a variety of organisms. Even in those instances in which vaginal smears show a uniform Grade I flora, other organisms can be obtained by cultural methods, particularly,

if a number of culture media suited to the growth of different types of organisms is employed. Among the more common inhabitants of the vaginal tract are certain staphylococci, streptococci, diphtheroids, and coliform organisms. Their presence in only small numbers in the normal vagina is very likely due to inhibition of growth by the high degree of acidity. It is probable that some of the simpler sugars in the vagina may be broken down by these organisms and some initial degree of acidity produced, which in turn is inimical to their further growth.<sup>31</sup> Their significance, however, lies in the fact that as soon as the normal protective mechanism is interfered with, either by physiologic or external factors, their growth will be greatly accelerated.

Special mention should be made of the yeast and yeast-like organisms which are so commonly found in the normal vagina. The growth of these organisms is favored by a high degree of vaginal acidity and the presence of fermentable carbohydrates in the vaginal secretion. Therefore, it is not surprising that they are most commonly found in the normal vagina usually associated with Döderlein's bacilli alone. Indeed, they tend to occur most frequently in pregnancy since, in the latter state the acidity and carbohydrate factors are most favorable.

### Summary

1. Extensive studies were made on the vaginal tract of more than 500 patients; included in this number were 37 normal patients in whom the studies were made three times weekly through one to three menstrual cycles. The special studies made included determinations of the pH of the vaginal mucosa, cytologic studies of vaginal smears, examination of smears stained for glycogen content, determination of the bacterial flora, and the study of vaginal biopsies.

2. The role of the estrogens as the major factor in controlling the histologic and cytologic features of the vaginal epithelium is reviewed, but evidence indicating that progesterone and perhaps other steroid hormones have an important influence is presented. Certain cyclic histologic changes were frequently noted on the biopsies, but in the main these were not nearly so clear-cut as the changes noted from cytologic study of vaginal smears.

3. Present evidence indicates that the estrogens are the dominant factor in causing the mobilization of glycogen in the vaginal epithelium; progesterone may aid in this process. Androgens appear to be an inhibiting factor in glyconeogenesis.

Glycogen is abundantly present in vaginal biopsies. A concentration of 2.5 to 3.0 mg. per cent was encountered in the upper part of the vagina and smaller concentrations in the lower part of the vagina. The metabolism of vaginal glycogen is not known, but various theories are discussed.

Vaginal biopsies prepared with Best's carmine stain were found to be highly suitable for demonstrating distribution of vaginal mucosa. Cyclic changes in glycogen content were far more easily noted in vaginal smears stained by an iodine method. It was found that the glycogen content of the superficial vaginal epithelium showed a tendency to increase throughout the cycle and then to fall in the late premenstrual phase, thus roughly approximating the estrogen excretion through the cycle.

4. The various methods for determining the pH of the vaginal secretion and mucosa are reviewed. Direct determination of the pH of the vaginal mucosa by the glass electrode method was chosen as most accurate and reliable. A special glass electrode is described which has been found to be highly satisfactory for this purpose.

In making 632 readings on 100 normal women, it was found that the pH varied from 4.0 to 5.0 in all except 3 per cent of the determinations.

A pH gradient was found to exist in the vagina in most patients. The highest acidity was generally encountered in the anterior fornix. The next highest readings were obtained in the middle third of the vagina; these were generally quite constant and most nearly approximated the pH of the vaginal secretion. Lower values were obtained in the lower third of the vagina, while determinations made in the posterior fornix usually varied considerably. In the 37 cases studied at frequent intervals, a periodic variation in pH was observed in many instances. The average readings indicate that pH gradually falls to reach its lowest point at the midcycle and then gradually rises to meet the highest values at the premenstrual stage.

5. The factors which influence the character of the vaginal flora are discussed. From available evidence it would appear that the vaginal pH is the strongest immediate factor determining the type of organisms present in the vaginal tract.

The vaginal pH and flora were correlated for a large series of patients and indicated that most of the patients with Grade I flora had a vaginal pH of 3.9 to 5.0 (range 3.9 to 6.0, average 4.56). Majority of patients with a Grade II flora fell in the pH interval 4.6 to 5.5 (range 4.0 to 7.0, average 5.09). In Grade III type the majority of the patients had a pH of 5.1 to 6.0 (range 4.0 to 9.0, average 5.54).

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## ACUTE ANTERIOR POLIOMYELITIS DURING PREGNANCY\*

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**A**CUTE paralytic anterior poliomyelitis has been observed as a complication of human pregnancy. This observation raises several questions: (1) Does pregnancy per se affect the susceptibility of the mother to the disease? (2) Is the disease transmissible from mother to fetus in utero? (3) Is the disease transmissible to the offspring through the secretions of the mammary glands? To our knowledge the problems presented by these questions have not been investigated experimentally. The present communication records experiments and results pertinent to these problems.

### Part I. Effect of Pregnancy Per se on Susceptibility of the Mother

A total of 75 cases diagnosed as paralytic anterior poliomyelitis acquired during pregnancy† have appeared in the literature (cases cited in Table I). Since the majority of these cases have been reported within the last few years, it may be that the small number of cases is due to incomplete reporting rather than to a rarity of this condition as indicated by the work of Aycock (1941). In 5 of the reported cases the records are so incomplete as to be of little value. Of the remaining 70 cases, one or more have been recorded for each month of the gestation period. Of these, 17.1 per cent occurred during the first trimester, 34.3 per cent during the second trimester, and 48.6 per cent during the third trimester.

*Experimental Method.*—A 10 per cent, unfiltered suspension of the virus of poliomyelitis was made from the glycerolated brain stems and spinal cords of cotton rats paralyzed by treatment with the Armstrong-Lansing strain. Each of the cotton rats in this experiment was given a single three-way inoculation (0.1 c.c. intracerebral, 0.5 c.c. subcutaneous, 0.1 c.c. intranasal) with the virus (see Table II).

Sixty-four cotton rats of comparable ages were used in this experiment. For convenience, the 28-day gestation period of these animals was divided into trimesters for the purpose of comparing the relative susceptibility at different stages of pregnancy. Three groups of animals have been observed. Group 1 includes the pregnant animals‡ with

\*Sponsored by The National Foundation for Infantile Paralysis, Inc.

†One case was reported by Foulkrod (1923) but, as McGoogan (1932) has already indicated, this was probably not a case of poliomyelitis. Aycock (1941) cited a case supposed to have been reported by Guttmann (1932) as one of poliomyelitis. A review of Guttmann's report indicates that this was a case of uncomplicated apical poisoning rather than of anterior poliomyelitis. Another case was reported by Peelen (1943) as having occurred in the fourth month of pregnancy. The evidence presented, however, does not justify including this case as one of anterior poliomyelitis.

‡We are indebted to Dr. C. C. Young and his staff of the Michigan Department of Health Laboratories, Lansing, Mich., for supplying the timed-pregnancy cotton rats used in this investigation.

TABLE I

CASE NUM- BER	AUTHOR AND YEAR	MONTH OF PREGNANCY	AGE OF MOTHER	PARALYTIC INVOLVEMENT
1	Schell, 1906	7	26	Lower extremities
2	Hartman, 1909*	4	?	?
3	Hartman, 1909*	7	?	?
4	Hartman, 1909*	7	?	?
5	Hartman, 1909*	8	?	?
6	Hartman, 1909*	8	?	?
7	Hartman, 1909*	9	?	?
8	Mueller, 1910	9	?	?
9	Mueller, 1910	9	?	?
10	Renault and Martingay, 1911	5	23	Lower extremities and abdo- men
11	Wickman, 1913	?	?	?
12	Zimmermann, 1914	9	22	All extremities, abdomen, and back
13	Miller, 1924	3	26	Lower extremities
14	Miller, 1924	6 ?	?	Left lower extremity, bladder, and rectum
15	Hornung and Creutz- feldt, 1930	9	?	Landry's ascending type with respiratory involvement
16	McGoogan, 1932	3	24	Right lower extremity
17	McGoogan, 1932	3	24	Both lower and right upper ex- tremities
18	McGoogan, 1932	3	32	Lower extremities and abdo- men
19	Brahdy and Lenarsky, 1933	2	19	Dower extremities, abdomen, and back
20	Brahdy and Lenarsky, 1933	4	23	Right lower extremity
21	Brahdy and Lenarsky, 1933	9	22	Lower extremities
22	Ehrenfest, 1933	7	18	Right lower and upper extremi- ties and face
23	Pette, 1936	3	?	Death due to respiratory in- volvement
24	Fischer and Stillerman, 1937	8	?	Lower extremities and abdo- men
25	Klein and Sittig, 1938	9	25	All extremities
26	Ruhl, 1939	9	27	All extremities, abdomen and back with respiratory and deglutition involvement
27	Morrow, Luria and Ridgewood, 1939	5	28	All extremities, abdomen, blad- der and rectum
28	Author unknown,† 1939	7	18	Respiratory involvement
29	Spishakoff, Golenterneck and Bower, 1941	8	22	All extremities with respira- tory involvement
30	Helms, 1941	5	35	Lower extremities and abdo- men
31	Helms, 1941	6	18	Left lower extremity and ab- domen and flexors of head
32	Helms, 1941	6	29	Right upper extremity
33	Helms, 1941	8	21	Both lower and left upper ex- tremities, abdomen and back

TABLE I—CONT'D

CASE NUM- BER	AUTHOR AND YEAR	MONTH OF PREGNANCY	AGE OF MOTHER	PARALYTIC INVOLVEMENT
34	Helms, 1941	9	36	Upper extremities, abdomen, back, and neck
35	Aycock, 1941	?	?	?
36	Aycock, 1941	?	?	?
37	Aycock, 1941	1	26	?
38	Aycock, 1941	2	Young	?
39	Aycock, 1941	3	24	?
40	Aycock, 1941	4	20	?
41	Aycock, 1941	4	30	?
42	Aycock, 1941	4-5	16	?
43	Aycock, 1941	5	19	?
44	Aycock, 1941	5	24	?
45	Aycock, 1941	5	27	?
46	Aycock, 1941	5	33	?
47	Aycock, 1941	6	?	?
48	Aycock, 1941	6	?	?
49	Aycock, 1941	6	16	?
50	Aycock, 1941	6	20	?
51	Aycock, 1941	6	35	?
52	Aycock, 1941	7	23	Death due to respiratory in- volvement
53	Aycock, 1941	7	25	?
54	Aycock, 1941	7	26	?
55	Aycock, 1941	7	26	?
56	Aycock, 1941	7	32	?
57	Aycock, 1941	8	26	?
58	Aycock, 1941	9	?	?
59	Aycock, 1941	9	22	Respiratory involvement
60	Aycock, 1941	9	23	?
61	Gillespie, 1941	7	18	Landry's ascending type
62	Newberger and Associ- ates†	9	22	Lower extremities, abdomen with respiratory paralysis
63	Kleinberg and Horwitz‡	?	18	All extremities, abdomen, back, and vocal cords
64	Kleinberg and Horwitz‡	?	26	All extremities
65	Kleinberg and Horwitz‡	2	24	Lower extremities
66	Kleinberg and Horwitz‡	3	24	Lower extremities, abdomen and bladder
67	Kleinberg and Horwitz‡	3	26	Lower extremities, abdomen, back and bladder
68	Kleinberg and Horwitz‡	4	19	Right lower extremity
69	Kleinberg and Horwitz‡	4	25	Lower extremities
70	Kleinberg and Horwitz‡	6	24	All extremities
71	Kleinberg and Horwitz‡	6	28	Right lower extremity
72	Kleinberg and Horwitz‡	7	?	Left lower extremity and ab- domen
73	Kleinberg and Horwitz‡	7	17	Left lower extremity
74	Kleinberg and Horwitz‡	7	21	Both lower and right upper extremities
75	Peelen, 1943	9	29	Both lower and left upper ex- tremities

\*Cited by Aycock, 1941.

†München. med. Wchnschr. 86: 160, 1939.

‡Personal communication from Kleinberg and Horwitz, 1942.

viable fetuses and those which had delivered viable young within twenty-four hours. Group 2 includes animals whose fetuses had been resorbed (autopsy). Group 3 includes virgin female cotton rats as controls.

*Results.*—As set out in Table II, the average incubation period and extent of paralysis in each of the three groups is not significantly different. This conclusion is justifiable in view of the fact that the incubation period and extent of paralysis of the individual animals in any one group show a wide variation.

It is of interest to note that the only animals which developed no symptoms of poliomyelitis were 3 out of 13 animals inoculated with the virus during the first trimester of pregnancy.

TABLE II

	NO. OF ANI- MALS	TIME OF INOCULATION	INCUBA- TION PERIOD (DAYS)	EXTENT OF PARALYSIS (EXTREMITIES)	NO. OF ANIMALS RESIST- ANT TO INOCULUM
Group 1	7	During first trimester	3.66 (2- 6)	3.66 (2-4)	1*
Pregnant cot- ton rats	5	During second trimester	6.40 (3-10)	3.20 (2-4)	0
with viable	6	During third trimester	4.66 (3- 6)	3.66 (2-4)	0
fetuses	6	Within 24 hrs. post partum	6.33 (3-13)	4.00	0
Summary Group 1	24		5.22 (2-13)	3.78 (2-4)	1*
Group 2	6	During first trimester	6.25 (5- 8)	3.50 (2-4)	2†
Pregnant cot- ton rats	8	During second trimester	4.88 (2- 9)	3.25 (2-4)	0
with re- sorbed	2	During third trimester	6.00 (5- 7)	4.00	0
fetuses					
Summary Group 2	16		5.43 (2- 9)	3.43 (2-4)	2†
Group 3	24		6.58 (3-12)	3.42 (2-4)	0
Virgin female cotton rats					

\*When subjected to a second three-way inoculation 20 days after the first, and a few hours after giving birth to her young, this animal became completely paralyzed following an incubation period of eleven days.

†These animals became completely paralyzed following a single three-way inoculation administered in one case fourteen days and in the other case twenty-one days after their first exposure to the virus.

## Part II. Intrauterine Transmissibility of the Virus

In the human being 6 cases which were regarded as prenatal anterior poliomyelitis have been collected from the literature (Lamy, 1894; McCarthy, 1907-1908; Fritsch, 1908; Batten, 1910-1911; and Potts, 1929). The diagnosis of anterior poliomyelitis (Heine-Medin's disease) in these 6 cases is highly questionable for the following reasons: (1) No disease resembling anterior poliomyelitis was diagnosed in the mother during the prenatal period of any of these cases. (2) The virus of poliomyelitis was never recovered from the excreta or from the tissues out of any of these cases nor from the mothers of any of these cases. (3) Several of these cases were diagnosed as anterior poliomyelitis only after they were well advanced in years and long after the acute stage of any such disease had subsided. (4) In none of these reports was it stated that an epidemic of poliomyelitis was prevalent in the community during the prenatal period of any of the 6 cases. In addition, it should be pointed out that a review of 75 cases of paralytic poliomyelitis ac-

quired during pregnancy (see Table I) failed to reveal a single instance in which a paralyzed mother gave birth to a child who developed clinical signs of poliomyelitis.

*Experimental.*—The fetuses from 15 cotton rats paralyzed following a three-way inoculation with the Armstrong-Lansing strain of the virus of poliomyelitis, were removed from the fetal membranes as rapidly as possible after the death of the mother (see Table III). The central nervous systems of the fetuses in each litter were made into a 10 per cent suspension with normal saline.\* Each of these suspensions were inoculated in the usual three-way manner into 2 or 3 previously untreated cotton rats. Of 31 animals so inoculated, 5 only were sacrificed because of clinical manifestations occurring within a period of time equal to the usual incubation period of the virus. Of these 5 animals, 2 only appeared to be clinically paralyzed. In no case were clinical manifestations exhibited by more than 1 out of the 2 or 3 cotton rats treated with the same inoculum. Microscopic sections from samples of the central nervous systems of the 5 animals which had exhibited clinical manifestations revealed no histopathologic changes suggestive of anterior poliomyelitis.

A further passage into previously untreated cotton rats was attempted from each of 4 out of the 5 animals which had exhibited clinical manifestations. This was accomplished by making a 10 per cent suspension of the central nervous system from each animal (small bits of tissue had been utilized for microscopic examination). Each of these suspensions were inoculated in the usual three-way manner into 2 or 3 previously untreated cotton rats (see Table III). Of 9 animals so treated, 1 only died. This animal exhibited no symptoms whatsoever of anterior poliomyelitis, and examination of serial sections from the entire central nervous system of this cotton rat revealed no evidence of the disease.

### Part III. Transmissibility of the Virus Through Mammary Secretions

Two mother cotton rats were inoculated with the virus of poliomyelitis in the usual three-way manner 24 hours after they had given birth to their young. The offspring remained with and received nourishment from their mothers until the latter expired with poliomyelitis. In the first case the mother lived for 8 days and in the second case for 11 days after the young were born. Each mother appeared to satisfy the nutritional demands of her offspring until about 48 hours prior to her death. Artificial feeding of the offspring was successful and they grew normally and without loss. The first litter consisted of 2 males and the second of 4 males and 2 females. None of the offspring showed any evidence of paralysis, nor did any of these animals show any resistance to intracerebral inoculations with potent suspensions of the virus administered 25 days after the death of the mother.

### Discussion

It is conceivable that during pregnancy an altered susceptibility to paralytic anterior poliomyelitis might result from an alteration in the permeability of the portal of entry of the virus and/or a change in the effective "internal resistance" (neutralizing substance, circulating virucidal substances, etc.) of the host. The fact that certain hormones

\*One fetus from each of 6 mothers paralyzed with poliomyelitis was preserved in formalin and prepared for histologic study. The microscopic sections revealed no histopathologic changes suggestive of poliomyelitis in the central nervous systems of any of these 6 fetuses.



1 FETUS NUMBER	2 MOTHER INOCULATED (DAY OF PREGNANCY)	3 MOTHER SACRIFICED (DAY OF PREGNANCY)	4 EXTENT OF MOTHER'S PARALYSIS	5 HISTOPATHOLOGY CNS OF FETUSES SEE COLUMN 1	6 ATTEMPTED PASSAGE FROM CNS OF FETUSES SEE COLUMN 1		7 HISTOPATHOLOGY CNS OF FIRST-PASSAGE ANIMALS SEE COLUMN 6
					NUMBER OF ANIMALS INOCULATED	RESULTS	
436	2nd	4th*	1, 2, 3, 4 plegia†		2	Both negative	
791	7th	9th	1, 2, 3, 4 plegia		2	<div> 1 negative  1 apparently completely  paralyzed </div>	
1023	4th	10th	1, 2 plegia		2	Both negative	
1020	7th	12th	1, 2, 3, 4 plegia		2	Both negative	
457	8th	12th	1, 2, 3, 4 plegia		2	Both negative	
456	11th	14th	1, 2 plegia		2	<div> 1 negative  1 expired without  paralysis </div>	Negative
939	14th	19th	1, 2, 3, 4 plegia	Negative	2	<div> 1 negative  1 expired without  paralysis </div>	Negative
1305	14th	20th	2, 3 plegia	Negative	2	Both negative	
940	14th	22nd	1, 2, 3, 4 plegia	Negative	2	Both negative	
943	14th	24th	1, 2, 3, 4 plegia	Negative	2	Both negative	
573	19th	25th	1, 2, 3, 4 plegia		2	Both negative	
621	21st	26th	1, 2, 3, 4 plegia	Negative	2	Both negative	
622	22nd	27th	3, 4 plegia	Negative	2	Both negative	
320	24th	28th	1, 2, 3, 4 plegia		2	<div> 1 negative  1 apparently completely  paralyzed </div>	Moderate gliosis
300	24th	29th	1, 2, 3, 4 plegia		3	<div> 2 negative  1 expired without  paralysis </div>	Negative

\*Expired.

†1 plegia = flaccid paralysis of left front extremity.

2 plegia = flaccid paralysis of right front extremity.

## III

8 RESULTS OF INOCULATING VIRULENT VIRUS INTO SURVIVING FIRST-PASSAGE ANIMALS SEE COLUMN 6	9 ATTEMPTED FURTHER PASSAGE FROM CNS OF QUESTIONABLY POSITIVE FIRST-PASSAGE ANIMALS SEE COLUMN 6		10 HISTOPATHOLOGY CNS OF SECOND-PASSAGE ANIMALS SEE COLUMN 9	11 RESULTS OF INOCULATING VIRULENT VIRUS INTO SURVIVING SECOND- PASSAGE ANIMALS SEE COLUMN 9
	NUMBER OF ANIMALS INOCULATED	RESULTS		
{ 1 paralyzed after 1st re- inoculation 1 resisted 3 reinoculations				
1 paralyzed after 1st re- inoculation	2	Both negative		{ 1 paralyzed after 1st reinoculation 1 paralyzed after 2nd reinoculation
Both paralyzed after 1st reinoculation				
Both paralyzed after 1st reinoculation				
Both paralyzed after 1st reinoculation				
1 paralyzed after 1st re- inoculation	2	Both negative		Both paralyzed after 1st reinoculation
1 paralyzed after 1st re- inoculation				
Both paralyzed after 1st reinoculation				
{ 1 paralyzed after 1st re- inoculation 1 resisted 3 reinoculations				
Both paralyzed after 1st reinoculation				
{ 1 paralyzed after 1st re- inoculation 1 resisted 3 reinoculations				
Both paralyzed after 1st reinoculation				
Both paralyzed after 1st reinoculation				
1 paralyzed after 1st re- inoculation	3	{ 2 negative 1 expired without paralysis	Negative	Both paralyzed after 1st reinoculation
2 paralyzed after 1st re- inoculation	2	Both negative		Both paralyzed after 1st reinoculation

1, 2, 3, 4 plegia = complete flaccid paralysis.

3 plegia = flaccid paralysis of right rear extremity.

4 plegia = flaccid paralysis of left rear extremity.

are present in increased amounts during pregnancy has stimulated a number of workers to speculate as to the relation of the endocrine glands to the occurrence of paralytic anterior poliomyelitis. In the human being pregnancy is characterized by an elevation in the levels of two hormones, estrogen and progesterone, which are present in normal individuals; and the addition of an entirely new substance, gonadotropin.

It has been said that the quantity of urinary estrogen (presumably an index of estrogen formation) in the human being rises at an increasing rate until parturition, after which it disappears in the course of a few days (Newton, 1939). At term, the total estrogenic substance excreted in the urine may be in amounts as high as 100,000 rat units daily (Freed, 1942).

The investigations of Aycock (1937-1940) indicate that the permeability of the nasal mucosa to the virus of poliomyelitis can be altered by preliminary treatment with estrogen. Schultz (1941) was unable to corroborate these findings. The studies of Jungeblut and his co-workers (1934) and Clark (1941) indicate that there is no apparent relationship between estrogen and the effective "internal resistance" of the host as judged by the occurrence of neutralizing bodies in the serum and resistance to intracerebral inoculations with the virus.

Urinary progesterone, excreted mainly as pregnandiol glucuronide, begins to rise during the first month of pregnancy and in the ninth month may have a value exceeding ten times that found in the luteal phase of the menstrual cycle (Newton, 1939). To our knowledge, the possible relationship of progesterone to the resistance of an individual to the virus of poliomyelitis has never been investigated.

Chronic gonadotropin (anterior pituitary-like hormone) appears in the urine of the pregnant woman within a few days after the first missed period. From twenty to fifty days after the missed period, tremendous quantities of this substance are present in the urine. Several hundred thousand rat units have been demonstrated to be present in one liter of urine obtained from a pregnant woman during this interval of time (Evans, Kohls, and Wonder, 1937). After this time the daily excretion remains at a fairly constant level, from 3,000 to 10,000 rat units, until termination of pregnancy, after which it disappears normally within four or five days (Freed, 1942).

Jungeblut and his co-workers (1934) stated that they were able regularly to neutralize the virus of poliomyelitis in vitro with sera from two pregnant mares obtained during the second trimester, and irregular results were obtained with crude prolan. The serum from pregnant mares obtained between the fiftieth and one hundred fiftieth days of pregnancy is known to contain large quantities of chorionic gonadotropin, whereas crude prolan used by Jungeblut probably contained a much smaller quantity of this substance.

Jungeblut and Engle (1934) subjected 23 immature rhesus monkeys to daily injections of 2 to 8 c.c. of prolan for from 9 to 30 days. Fifteen of twenty-nine samples of serum obtained from these animals after treatment with prolan neutralized either partially or completely, the virus of poliomyelitis in vitro. Four of these animals either resisted completely an intracerebral inoculation with the virus of poliomyelitis or contracted the disease only after a prolonged incubation period.

A review of the literature (Table I) reveals that of the cases of paralytic poliomyelitis in the human being which were contracted during pregnancy, only 17.1 per cent occurred within the first trimester. It is during this third trimester of pregnancy in the human being that the formation of chorionic gonadotropin is at its peak.

In this connection, it is of interest to note that the only pregnant cotton rats of our group resistant to the first inoculation with the virus of poliomyelitis were three which were inoculated between the fourth and seventh days of pregnancy. Although we have no information relative to the formation of chorionic gonadotropin during pregnancy in the cotton rat, from studies on other species it is probable that, if it is formed at all, its production may reach a peak near the time these animals were inoculated. That these animals were temporarily resistant to the inoculum only is demonstrated by the fact that each became completely paralyzed following a second three-way inoculation with the virus of poliomyelitis administered between 14 and 21 days later. It is probable that chorionic gonadotropin was not present in significant quantities in these animals at the time of the second inoculation, since one rat had delivered her young and the other two animals had resorbed their fetuses. The incubation period following the second inoculation with the virus was within normal limits.

We do not believe it to be an accident of experimentation that 3 out of 13 cotton rats inoculated during the first trimester of pregnancy were resistant to their first exposure to the virus of poliomyelitis. During the past two years we have subjected over 300 previously untreated and nonpregnant cotton rats of all ages to three-way inoculations with the Armstrong-Lansing strain of the virus of poliomyelitis. Of these, 2.86 per cent of the males and 2.53 per cent of the females resisted their first exposure to the virus and succumbed, completely or partially paralyzed, to a second three-way inoculation. In contrast to these figures, 23.08 per cent of the pregnant cotton rats inoculated during the first trimester of pregnancy resisted the virus.

It would appear from the information at hand, that chorionic gonadotropin, or some substance associated with the formation or metabolism of this hormone, might play a role in increasing the resistance of the pregnant female during the first trimester of pregnancy to the virus of poliomyelitis. It should be emphasized, however, that this possibility is suggestive only. The greater number of cases of the disease

in the human being acquired during the latter months of gestation might result from the diminished secretion of chorionic gonadotropin or might be due entirely to other factors peculiar to the latter months of pregnancy.

We believe that the experiments reported earlier in this communication indicate that in the cotton rat infective quantities of the Armstrong-Lansing strain of the virus of poliomyelitis are not transmitted from a mother to the nervous tissues of a fetus in utero. It appears further that the virus is not transmissible to the offspring through the secretions of the mammary glands. These findings were not unexpected in view of the fact that an overwhelming majority of attempts to recover an infective quantity of virus from the blood of human beings or of experimental animals suffering from paralytic poliomyelitis have been unsuccessful. Finally, should the virus of poliomyelitis actually pass through the placenta it might be that it would be attenuated or even neutralized by the activity of virucidal substances peculiar to this organ. McKhann and Chu (1933) prepared an extract from the placenta which contained only traces of female sex hormone, and stated that this preparation was capable of neutralizing the virus of poliomyelitis in vitro. Tezner and Goldhamer (1933) and Jungeblut, Meyer, and Engle (1934) called attention to the fact that poliomyelitis-virucidal substances could be demonstrated in placental extracts in certain cases where it was absent in the maternal serum. Whether this virucidal substance in the placenta is capable of inactivating the virus of poliomyelitis in vivo as well as in vitro is unknown.

### Conclusions

1. Some evidence was presented which may indicate that chorionic gonadotropin, or some substance associated with the formation or metabolism of this hormone, might play a role in increasing the resistance of the pregnant female during the first trimester of pregnancy to the virus of poliomyelitis.

2. There was no evidence that infective quantities of the Armstrong-Lansing strain of the virus of poliomyelitis were transmitted from the mother to the nervous tissues of the fetus in utero, or from the mother to the nervous tissues of her offspring through the secretions of the mammary glands.

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## CARCINOMA OF THE CERVIX, END RESULTS\*

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ONE of us, in 1931, made an evaluation of high voltage roentgen therapy in the treatment of carcinoma of the cervix. The study was based upon the duration of life of 437 women with cervical cancer, who had been treated in the radiologic department of the Philadelphia General Hospital, and followed until their deaths.<sup>1</sup> This unconventional approach was adopted because of the peculiar character of the material available in our clinic. Lesions less advanced than Stage III were encountered so infrequently that too few patients survived the five-year period to provide material for reliable statistical comparisons. Of the 437 cases included in the above report, there were only one in Stage I and three in Stage II (Schmidt's classification). Our primary purpose in the investigation was to determine whether high voltage x-ray therapy was of any value in the treatment of this disease. We were also interested in learning whether subsequent reports based on the five-year survival rate, would confirm the impressions obtained from our study.

The "five-year arrest" has for years been the standard by which the value of treatment for carcinoma of the cervix has been measured. Though undoubtedly the best basis for comparison of therapy so far provided, it has many limitations. Treatment with a high primary mortality rate, or subject to frequent undesirable complications, though it result in many "five-year cures," may be less desirable than another method involving a lower initial mortality and fewer complications, but with a smaller number of patients symptom-free five years after treatment. The objective in cancer therapy should be not only to arrest permanently a great percentage of cases, but also to render the incurables useful and comfortable for as long as possible. We believe, therefore, that the duration of life after admission is, per se, a proper feature to consider in appraising the results of any form of therapy. Subsequent reports by Scheffey<sup>2</sup> and others based on "five-year arrests" have confirmed the findings of our original study.

In our clinic previous to 1928, cancer of the cervix in Stages I, II, and III, was treated with radon in a cervical T tube, with filtration of 0.5 mm. silver, 1 mm. brass and 2 mm. rubber. The dosage was 2,400 mc. hrs. Tragic accidents such as perforation of the uterus, rapidly spreading peritonitis, and septicemia following the use of radon in Stage IV cases, caused us to discontinue radon therapy in such ad-

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vanced lesions, and most of these patients received no treatment at all. Some were given applications of high voltage roentgen therapy through two or four external ports. In the light of our present knowledge, the dosage of this external irradiation was invariably inadequate.

From 1928 to 1931, all patients whose general condition permitted, were treated with high voltage therapy, regardless of the extent of the disease. The usual dosage consisted of 1,600 to 1,800 r. (air) to each of four to six fields, 15 by 20 cm., depending upon the size of the patient. In the late stages, this was the only form of treatment given. Lesions in the first, second and third stages were treated with radon in the cervical and uterine canal, radon against the vaginal portion of the growth, and high voltage roentgen rays. The intracervico-uterine application was made with a filtration of 0.5 mm. silver, 1 mm. brass, and 2 mm. rubber. The capsules in tandem varied in number depending on the length of the uterine cavity. The dosage ranged between 2,000 and 3,000 mc. hrs., depending upon the depth of the cervical canal. The vaginal application of radon was made in three sittings. 1,000 mc. hrs. of radon with a filtration of  $\frac{1}{2}$  mm. silver, 3 mm. lead and rubber (approximately equivalent to 2 mm. of platinum) at a distance of 1 cm. were applied transversely against the cervical growth and into each vaginal fornix, to provide a three-directional cross-fire, totaling 3,000 mc. hrs. The high voltage x-ray therapy was administered with the four- to six-field technique developed by Weatherwax and Widmann<sup>3, 4</sup> of our clinic.

Soon after adopting the policy of treating Stage IV cases with high voltage x-ray therapy alone, but in adequate dosage, we sometimes observed rapid regression of both the primary tumor and the parametrial infiltration, so that the cervix recovered more or less of its mobility. Since 1931, many Stage IV patients responding favorably in this respect were subsequently treated with the standard dosage of radon into the uterine and cervical canals, and against the vaginal portion of the cervix, and six to eight weeks later a second course of high voltage radiation was given. Since 1938, an ever increasing number of our patients have also been treated with transvaginal high voltage x-ray therapy. In other respects our technique from 1931 to the present time has been identical to that employed from 1928 to 1931.

During this later period, 1931 to 1942, 579 additional patients, treated on the radiologic service of Philadelphia General Hospital, have died. It seems desirable at this time to compare the results secured in this second group with those obtained between 1922 and 1931, when different radiologic techniques were practiced, and to learn if possible the reliability of statistics based on the duration of life after admission.

Since 1931, five patients in Stage I have died. One of these patients, aged seventy-two, died thirteen days after admission from gangrene of the foot due to arteriosclerosis, without treatment for her carcinoma. A second patient, whose lesion was in the first stage at the time of treatment, is of passing interest because of surprising findings at

TABLE I. CASES ARRANGED IN STAGES (SCHMITZ)

CARCINOMA OF CERVIX	
END RESULTS	
STAGE	NO. OF CASES
I	5
II	27
III	168
IV	260
V	119
Total	579

autopsy. She lived only ten months after her treatment, and at the time of her death, metastases were found in the lungs, liver and peritoneal cavity, yet the primary lesion had been destroyed and there was no discoverable involvement of her parametrial tissues by the growth. Four treated patients lived an average of 9.5 months after treatment as compared with the single Stage I patient in our earlier group who survived for twenty-one months.

Of the 27 patients in Stage II, one refused any treatment and another, after having been treated with radon, refused high voltage x-ray therapy. The average life span after admission for the 20 patients in this stage, who were treated with high voltage x-ray therapy and radon, was 17.2 months. Five other patients whose treatment, for various reasons, was incomplete, averaged only 6.8 months of subsequent life. In our previous report, three patients in Stage II, who had died, lived an average of 13.3 months.

Fig. 1 is concerned with two groups of patients in Stage III. The cross-hatched columns representing patients admitted before 1931 and the solid columns, those admitted since then and numbering 166. Eleven of these patients received no treatment at all, and their average life duration was 4.6 months. Twelve cases, treated only with radium, lived 9 months after admission. Ninety-nine cases receiving external roentgen irradiation and radon, died an average of 18.8 months after treatment; whereas 46 patients who were treated only with high voltage x-rays, applied externally and in some cases transvaginally, lived an average of 10.8 months. By comparing the survival time of these women with those in our earlier group, it will be seen that the untreated cases which occurred in approximately the same proportion, lived just a little longer. Eight of these refused treatment and three died of other causes before treatment could be started. The twelve patients who were not given high voltage x-ray therapy, had refused this supplemental treatment. The average duration of their lives was slightly higher than in those of the first series. The ninety-nine patients receiving our standard treatment with high voltage x-ray therapy and radon, lived an average of 18.8 months, an improvement of seven months (40 per cent) over the group reported in 1931. Forty-six patients treated with only high voltage x-rays externally and transvaginally, lived an average of 10.8 months, an improvement of almost four months (50 per cent), when compared with the 1931 cases. It should be recalled that the present series received a higher dosage of external irradiation and some, in addition, transvaginal irradiation.

In Stage IV, there were 260 patients admitted since 1931. (Fig. 2.) Eighty-five of these received no treatment, either because they refused it, or because their physical condition precluded even the administration of external high voltage x-ray therapy. The average duration of life in the untreated cases was 1.8 months. Four patients had intravaginal applications of radon with 0.5 mm. silver and 5 mm. lead filtration at a distance of 1 cm. and lived an average of 8.66 months. In ten patients, following high voltage x-ray therapy, the tumor had regressed so that the cervix was again movable, and these were subsequently treated with radon. These lived an average of 13 months. One hundred and sixty-one cases, treated with external high voltage therapy alone, lived an average of 7.9 months. Fig. 2 shows that while the average duration of life in the Stage IV cases who received no treatment was practically the same as in the group reported previously, those treated with radon heavily filtered, and applied at a distance, lived more than twice as long as the Stage IV cases in the 1931 group

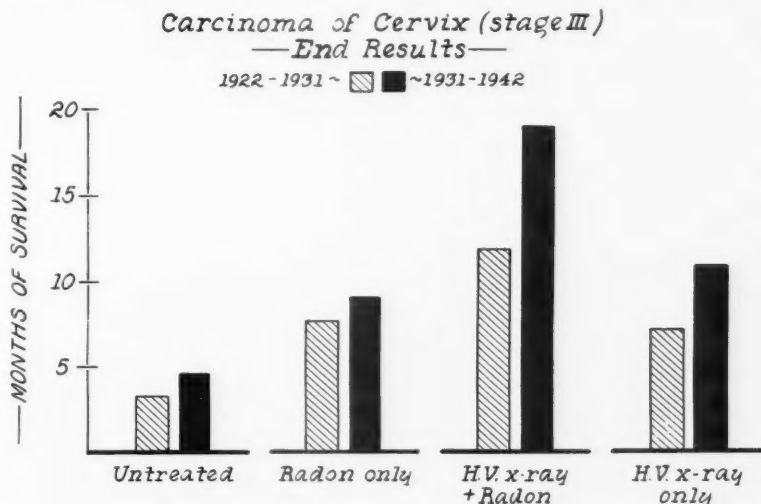


Fig. 1.—Comparison of the duration of life after different forms of treatment. In the earlier series the radon and x-ray dosages were smaller and the filtration was less. Few patients were untreated in either series.

who were treated with lightly filtered radon applied intracervically. The patients of the present study in Stage IV treated with x-ray therapy and radon also lived twice as long as those previously reported. It is our opinion that this increased survival time was due to the fact that the radon was applied only in those cases where high voltage x-ray therapy was followed by localization of the primary tumor, and disappearance of the parametrial infiltration. The fixation of the pelvic organs in these instances may have been due to inflammatory exudate, rather than to extension of the neoplasms. Aware that in some clinics these patients would be reclassified into Stage III, we believe such practice to be confusing and retain the classification decided upon when the lesion was first seen by us. The 161 patients treated with high voltage x-ray therapy alone, were those in whom sufficient regression to make them suitable for later radon application failed to occur after high voltage x-ray therapy. It is therefore not surprising that in this series the patients treated with x-rays alone had a shorter survival time than those who subsequently received radon, or that



there was little difference in the life span after admission with x-rays alone in the two series.

One hundred and eighteen cases, about 20 per cent of the patients admitted since 1931, were classified as in Stage V. (Fig. 3.) All of these women were sent to our clinic from other hospitals in the Philadelphia area, and a large proportion of them were unsuitable for even external irradiation with high voltage therapy. There were 60 such cases who survived an average of 2.4 months. No Stage V lesions in our later group were treated with radon alone. Seven patients after being treated with high voltage x-ray therapy were regarded as suitable for subsequent radon irradiation. Their average survival time was 14.1 months. The remaining 52 patients were treated with high voltage x-ray therapy only. Their average life duration after admission was 12.4 months. In Fig. 3, it will be seen that the average duration of life of 2.4 months is approximately that observed in untreated Stage V cases in our earlier report. The average duration of life after admission in those treated with radon and high voltage therapy is only slightly more than that in the first series. That the patients treated with high voltage x-ray therapy only, survived almost twice as long as those previously reported may be due to the fact that more adequate dosages were applied.

*Carcinoma of Cervix (stage IV)*  
—End Results—

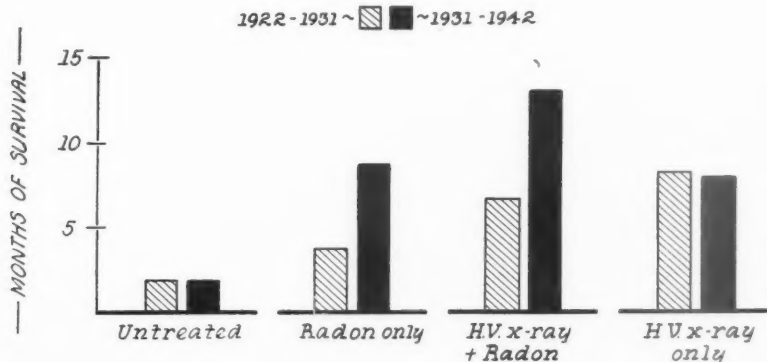


Fig. 2.—Comparison of the duration of life after different forms of treatment. In the earlier series the radon and x-ray dosages were smaller and the filtration was less. Untreated patients survived equally long in both series.

The present report, based on the histories of 580 patients suffering from carcinoma of the cervix, again demonstrates the value of high voltage roentgen therapy in the treatment of this disease. The importance of the later observations is enhanced by comparing these results with those of the earlier report concerning 437 patients; a grand total of 1,007 women suffering from cancer of the cervix, who died on the radiologic service of the Philadelphia General Hospital since 1922. Stage IV lesions, treated with external irradiation of high voltage x-ray therapy alone, lived longer than those treated with lightly filtered radium alone. The best results, however, were secured in the group who, after regression of the primary lesion had been brought

about by preliminary high voltage x-ray therapy, were subsequently treated with heavily filtered radon at a distance of 1 cm. Since this fact became apparent, it has become our policy to administer external high voltage x-ray therapy preliminary to the radon application in every case of carcinoma of the cervix. The longer duration of life in patients in the recent series who were treated with high voltage x-ray therapy, regardless of the stage of the disease, we believe can be attributed to the fact that these were given more adequate dosage than those of the 1931 study. Our findings in relation to the patients of both series who received no treatment at all, approximate each other so closely that we feel justified in recommending this method of study when it is desirable to evaluate the results of treatment of carcinoma of the cervix without waiting for a large number of patients to have passed the five-year period.

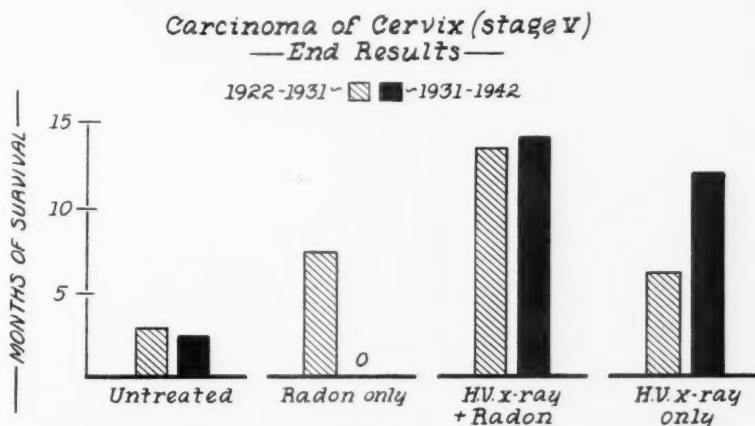


Fig. 3.—Comparison of the duration of life after different forms of treatment. In the earlier series the radon and x-ray dosages were smaller and the filtration was less. None in the later series were treated with radon alone.

### Summary

1. When the general condition of the patient permits, every case of carcinoma of the cervix should be treated with some form of irradiation therapy.
2. External high voltage roentgen therapy is always beneficial and safe for even the most advanced stages of the disease.
3. In many apparently advanced lesions, preliminary x-ray therapy will result in sufficient regression of the lesion that radon may be applied subsequently to great advantage.
4. Heavily filtered radon applied at a distance of one centimeter, results in better palliation than the highly filtered radon in contact application.
5. By observing the duration of life after admission to service in patients who died from carcinoma of the cervix, a satisfactory indication of the value of various forms of therapy may be obtained.

### Factors Employed in High Voltage Roentgen Therapy

Two hundred kv., 20 ma., 50 cm. F.S.D., 0.5 mm. Cu. plus 1.0 mm. A.C. filter, half-value layer 0.95 mm. Cu., 15 by 20 cm. fields, 4 to 6 ports, all fields directed to the cervix. Dose 2,000 r. (air) approximately 3,000 r. (tissue) delivered to the tumor. Patients treated on alternate days giving 150 r. to each of 4 fields until tumor receives 3,000 r. (tissue). Approximately three weeks.

### References

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4. Weatherwax, J. L., and Widmann, B. P.: Physical Factors in Radiation Therapy and Their Clinical Application, *Radiology* 12: 297-308, 1929.

### Discussion

DR. LEWIS C. SCHEFFEY.—With a large number of patients having advanced cervical lesions (Groups III, IV, and V), Dr. Behney and Dr. Howson have clearly shown how the duration of life can be prolonged by adequate irradiation treatment. I would be interested also to have Dr. Behney tell us approximately what his five-year survival rate has been in these patients with such advanced disease.

Our experience in the uterine carcinoma clinic of the department of gynecology at Jefferson Medical College Hospital has been similar. Our most recent report, published in *Radiology* in May, 1943, covers a sixteen-year survey of nearly 300 patients treated between 1921 and 1937. Of these, less than 40 per cent were treated with both radium and x-ray, for it was only since 1931 that x-ray began to be used at all frequently in conjunction with radium. Not until 1934 to 1935 was x-ray employed as a routine procedure prior to the application of radium. Even so, the five-year survival rate for patients treated in the latter fashion is substantially better when compared to those patients treated differently: i.e., 30 per cent (relative cure rate), as opposed to 13.9 per cent when the x-ray was used subsequently, and 16.6 per cent when it was used both before and after radium. It will be of vital interest to us to note whether or not the continued use of the present method will maintain this improved survival rate when our next five-year report is presented in 1946 to 1947, especially since transvaginal therapy has been employed as an added port during the past two years.

DR. BERNARD P. WIDMANN.—As a radiologist I can allude to some of the technical procedures which we carried out and which, I believe, contributed something to improving the end results. Since 1931, we have carried out a statistically and predetermined plan of treatment so that if a patient completed a series of treatment we knew how much she had had. Prior to that, we had had a manifold experience with varied techniques.

It is impossible to give more than the equivalent of about 2,000 r. or sometimes 3,000 r. tissue dosage. If you give more than that in about three to four weeks, you reach a treatment dose beyond the capacity of the individual. In the advanced group of cases we think it is better to give a series of x-ray treatments before radium is given. The interval between the two is about six weeks.

When the radium is finally given in a Stage III or IV case, we feel that it is a mistake to give a treatment with a single capsule, which would cover a length of 20 to 24 millimeters. If it is possible to get into the uterine canal and extend the treatment to 9 centimeters we irradiate a larger area. When you give 2,000 or 3,000 milligram hours you are giving a very large dose—as much as 30 to 45 erythema doses. It must be remembered that ninety per cent of the irradiation is absorbed in the first

centimeter of tissue. If you give a larger dose, 3,000 to 4,000 milligram hours, the irradiation extends beyond that.

There are some cases where you can supplement with a vaginal radium tampon against the cervix. If you use a filtration of 2 millimeters of platinum at 1 centimeter distance, you can give as much as 3,000 milligram hours but it will give a reaction so that two to three years later you have a marked stenosis of the posterior half of the vaginal vault. Because of that possibility, we think it is better to divide the treatment in one-third or one-half, and possibly you will be able ultimately to give as much as 4,000 milligram hours.

We are also trying out the so-called intracavitary treatment with cone and x-ray. We use it only in advanced cases, but when you get a frozen pelvis, you cannot twist the cone around in the pelvis. I do not know whether vaginal treatment with the high voltage x-ray is going to be equal to the radium.

With the higher voltage and a thicker filter you get a better depth dose but the quality of radiation does not have a better effect on the carcinomatous tissue than the 200,000 volt. The wave length which the dermatologist uses is also just as effective, but there is the difference in getting the depth dose. If the patient is measured accurately, you can add more fields of treatment and deliver just as effectual irradiation if you use the new supervoltage machine. The point is, to deliver an equivalent of about 3,000 tissue r., repeat about six to eight weeks later, and then supplement it with radium. I think you can then consider you have given the patient the benefit of everything which x-ray and irradiation can offer.

DR. OWEN J. TOLAND.—I was interested to see the short survival rate in the grade four and five carcinomas. This raises a point of extreme importance which was not mentioned. If with this combination of radiation methods the survival rate is as low as fifteen months, I would like to raise the question of whether Dr. Behney thinks those patients are more comfortable with treatment. If not, we had better drop radiation therapy and treat with acetone and morphine.

DR. BEHNEY (closing).—When the original paper (1931) concerning this unconventional method of evaluating treatment for carcinoma of the cervix was written, the benefits of high voltage x-ray therapy were, to say the least, viewed with suspicion by the majority of gynecologists. While we, at Philadelphia General Hospital, were convinced of its value, and had treated many patients with this agent, there were too few who survived five years after treatment to furnish satisfactory statistics. The object of the study was to determine whether high voltage therapy was of *any* value in the treatment of this disease. This, I believed, would be apparent if patients so treated lived longer than a control series of patients, with a similar degree of involvement, who had not received x-ray therapy. Subsequently, as mentioned, reports based on five-year survivals of patients treated with high voltage therapy were in accord with the impressions gained from the original study.

The present presentation, a continuation of the original study, includes approximately five hundred additional cases, still provides a number far short of that considered desirable by statisticians. We hope that other gynecologists will review their records in a similar manner. If this method of evaluation were proved acceptable, it would enable one to appraise the value of treatment for cancer without waiting from five to ten years to collect a large number of five-year survivals.

In addition to those considered in this report, we have a number of patients who have lived beyond the five-year period. Many of them are still living, some twenty years after treatment. Since this method of evaluation is based on the duration of life after treatment, living patients cannot be included here. In reply to Doctor Toland, I should like to say that in our opinion patients treated with high voltage therapy have definitely less pain than those who do not receive it. This point has been stressed in other reports by us, as well as by many other observers.

## SALMONELLA INFECTION IN GYNECOLOGY\*

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HUMAN infection with the *Salmonella* bacilli have been reported much more frequently in recent years. It was believed that the characteristic syndrome produced by this organism was gastroenteritis or "food poisoning." However, as a result of improvement in bacteriologic technique, it is evident that infection by these organisms is much more frequent and may produce a variety of clinical syndromes. More than one hundred types of *Salmonella* organisms are now recognized by cultural and serologic methods. They are divided into six main groups.

The most common organism resulting in clinical infection is *Salmonella typhi* *murium*. It was found 369 times among 1,000 human *Salmonella* infections at Beth Israel Hospital in New York City.<sup>1</sup> Septic infections, enteric fever and gastroenteritis are the most common types of infection encountered. Although it is still generally believed that these infections are due to the ingestion of contaminated food, it is possible that they may be transmitted "through the handling of animal carcasses, bathing in polluted waters and by transfer from man to man either directly, by insect vectors or by contact infection from food, dishes or nursing bottles."<sup>2</sup>

Pelvic infection caused by the *Salmonella* bacilli have been recognized with extreme rarity. Two cases of postabortal sepsis<sup>3, 4</sup> and single cases of post-partum sepsis,<sup>5, 6†</sup> infected fibromyoma uteri<sup>7</sup> and infected hematocele<sup>8</sup> have been reported in addition to three cases of infection of the tubes and ovaries.<sup>9-11</sup> (Table I.) To these we would like to add two additional cases of salpingo-oophoritis caused by a *Salmonella* bacillus.

### CASE REPORTS

CASE 1.—A. W., a 33-year-old nullipara, was admitted to the Beth Israel Hospital complaining of right lower quadrant pain. One year ago, she experienced severe right lower abdominal quadrant pain and fainting for which she was hospitalized elsewhere. Since that time, she has had repeated attacks of abdominal pain and fever, attributed to "inflamed tubes." In the past six months, she had noticed a purulent discharge from the rectum. She had been married six years and had never been pregnant. Menses began at 14, occurred regularly every 28 days and lasted 3 days. The last menstrual period occurred 18 days before admission. The past history was irrelevant.

\*This is part of a study of the bacteriology of tubal infection undertaken by a grant from the Greater New York Fund.

†(6) Refers to Roth's case.



TABLE I

AUTHOR	DIAGNOSIS	ORGANISM	SOURCE OF INFECTION	AGGLUTINATION TEST	REMARKS
Bornstein Saphra Strauss	Septic abortion	<i>S. Cholerae Suis</i>	Not stated		Positive blood culture
Ten Broeck Li Yu	Septic abortion	<i>S. Paratyphoid C</i> (?)	Not stated	Positive	Positive blood culture
Roth	Puerperal	<i>S. Suipestifer</i>	Not stated		Suipestifer obtained from empyema subsequent to puerperal sepsis
Gray	Infected myomas	<i>S. Suipestifer</i>	Not traced	Weakly positive	Prolonged febrile illness with positive blood culture
Brown	Bilateral pyosalpinx	<i>S. Newport</i>	Not traced	Positive	Illness of one month preop.; discharged 30 days postop. Blood culture sterile
Herring Nicholson	Acute bilateral salpingitis	<i>S. Cholerae Suis</i>	Handling of infected pigs?	Positive	Prolonged postop. course. No blood culture
Jager Lamb	Right salpingitis and pelvic peritonitis	<i>S. Suipestifer</i>	Not traced	Positive	Ill 4 days, diagnosis of acute appendicitis
Brown Biddle	Infected hematocele	<i>S. Suipestifer</i>	Not traced	Positive	Positive blood culture

On physical examination, she appeared to be chronically ill and moderately anemic. There was tenderness in the right lower abdominal quadrant and a sensation of an ill-defined mass.

On vaginal examination, the external genitalia were normal; cervix conical, the fundus of the uterus was anteфлекed, normal in size and to the patient's left. The cul-de-sac was filled with a hard, globular mass continuous with that felt abdominally. This mass was somewhat irregular and not particularly tender.

Temperature 99.6° F., pulse 90, respiration 24, blood pressure 120/70, Urine showed a faint trace of albumin; rare red and white blood corpuscles, hemoglobin 98 per cent; red blood corpuscles 4,600,000; white blood corpuscles 6,500; polys 80 per cent; sedimentation rate 30 mm. in 45 minutes.

Following vaginal examination on the third day of admission, temperature rose to 102.4° F. and for four weeks varied between normal and 102° F. At this time, two distinct masses were palpable on vaginal examination, the one to the right being somewhat globular and cystic, whereas the one to the left was sausage-shaped.

The sedimentation rate varied from 15 mm. to 40 mm. in 45 minutes. The hemoglobin dropped to 70 per cent and red blood corpuscles to 3,500,000. The white blood corpuscle and differential count remained within normal limits. Smears and cultures of the cervix and urethra were negative for gonococci. Blood cultures were negative.

Since no improvement had been evident following one month of palliative therapy and the mass seemed to be pointing in the cul-de-sac, a posterior colpotomy was performed. No pus was obtained. For ten days following colpotomy the temperature curve seemed to be lower, but then daily rises in temperature, 101° F. to 102° F. recurred.

For the following five weeks she was treated with a variety of agents. Bed rest in Fowler's position, high caloric diet, forced fluids, insulin and transfusions were given. Sulfadiazine was attempted but had to be discontinued because of marked anemia. Injections of aolan produced a transient lowering of the fever. Vaginal diathermy was administered. Although her temperature gradually receded, she again complained of lower abdominal pain and the sedimentation rate remained persistently elevated, varying from 20 to 50 mm. in 45 minutes.

As there seemed to be no improvement in her condition, a laparotomy was performed eleven weeks after admission and seven weeks after the colpotomy. At this time the sedimentation rate was 38 mm. in 45 minutes. The blood count was normal except for a moderate anemia. The temperature level was about 100° F. At operation the right ovary was the site of an abscess about 12 cm. in diameter. The right tube was stretched over this abscess and was elongated, thickened and chronically inflamed. The left tube was thickened and adherent to the posterior wall of the uterus. A loop of ileum and the sigmoid were densely adherent to the abscess. The adhesions were dissected free from the mass and the right tube was cut away from the uterus, thereby exposing the ovary which was separated by blunt and sharp dissection from the surrounding structures. When the mass was almost completely mobilized it ruptured and a large quantity of foul-smelling pus escaped. Culture taken. A supracervical hysterectomy and bilateral salpingo-oophorectomy was performed. The posterior lip of the cervix was then split through its entirety and the cervical cuff removed from the vagina. A Mikulicz drain was inserted into the

vagina and peritonealization secured. Ten grams of sulfanilamide powder were left within the abdominal cavity.

*Pathological Report.*—(Dr. Plaut). Hyperemic, rather small body of uterus, 5 cm. high, tubal angles 5 cm. apart, anteroposterior diameter about 3 cm. Left tube and ovary are attached. They are bound together by adhesions and form a soft, irregularly ovoid mass, 4.5 by 3 by 2 cm. The uterine cavity is normal in width, the endometrium is thin, moderately hyperemic. There are several small myomas. The abdominal ostium is closed, the remnants of the fimbriae are attached to a star-shaped scar. The ovary which is adherent is edematous. Large adnexal mass consisting of a flat ovoid portion, 8 by 7 by 3 cm. and one having the shape of tube which is 11 cm. long. The large ovoid mass, after fixation, consists of a thick-walled cyst with thick yellowish festooned lining. On cross sections of the tube, the lumen cannot be distinguished. The cut surfaces appear spongy, partly homogeneous and grayish.

*Microscopic.*—Characteristic picture of severe chronic salpingitis with growing together of inflamed folds. Large areas in the outer layers are occupied by leucocytic inflammation. In the one tubal angle, the folds are moderately thickened and the number of nuclei in them is increased. Most of these nuclei, however, are spindle-shaped. The outer layers are more cellular than normal, with some round nuclei. The other tubal angle is practically normal. There are old tuboovarian adhesions and there is some chronic inflammation in the ovary. The endometrium is rather thin, partly bloody. It corresponds to an early proliferative phase. The cervix is not unusual.

*Diagnosis.*—Chronic salpingo-oophoritis. Small myomata uteri. The postoperative course was uneventful except for infection of the wound which was noted at the upper and lower angles on the ninth postoperative day. A considerable amount of pus was evacuated. The patient was discharged on the thirtieth postoperative day with a normal temperature. The abdominal wound was clean. The abdomen was soft with no tenderness or pain present. On vaginal examination, the stump of the cervix was felt to be high in the cul-de-sac and surrounded by an area of induration which was not tender or painful.

#### Bacteriology:

Dr. E. Seligman.—Smear of the pus recovered at operation showed gram-positive cocci, gram-positive rods, gram-negative rods, gram-negative extracellular diplococci, and polymorphonuclear leucocytes.

*Salmonella typhi murium* was grown from the pus in the tuboovarian abscess. A positive culture of this organism was also obtained immediately postoperatively from the patient's stool and on the ninth postoperative day from the pus of the wound infection. The stool was still positive for *Salmonella* at the time of discharge, but became negative three months later. Agglutination test for *typhi murium* was positive in a dilution 1:320.

She was seen one month later at which time she was completely free from symptoms; she had gained weight; the wound was well healed; the stump of the cervix was high up and the induration surrounding the cervix, noted at the time of discharge, was much lessened in amount.

CASE 2.—M. W., a 28-year-old divorcee, was admitted to Beth Israel Hospital with the chief complaint of bilateral lower abdominal pain prior to and during menstruation for the past three years. She had been divorced 5 years ago. Three years ago she had had an attack of acute

lower abdominal pain with fever and since then she had had occasional attacks of pain, fever and severe dysmenorrhea. She was gravida v, para iv, last pregnancy five years ago. Menses began at 12, were regular every 28 days and lasted 4 to 5 days. There was no increase in the amount of vaginal bleeding. The last menstrual period was ten days before admission. Appendectomy had been performed thirteen years ago. Temperature 99° F., pulse 80, respiration 24, blood pressure 115/80. Physical examination was normal except for the pelvic findings. There was a well-healed right rectus scar. There was no abdominal pain, tenderness or mass present. Multiparous vaginal introitus. The cervix was enlarged and bilaterally lacerated. Motion of the cervix produced some pain in the left lower abdominal quadrant. The uterus was normal in size, anterior in position and somewhat fixed. There was tenderness in both fornices with some thickening of the left tube.

The urine, blood count and sedimentation rate were within normal limits. Blood cultures were not done.

A diagnosis of chronic salpingitis was made and the patient was operated upon three days after admission. At operation both tubes were inflamed and thickened and there were numerous filmy adhesions between the tubes and ovaries. A right parovarian cyst, 1 cm. in diameter, was present. The uterus was normal in size, shape, and position. Both ovaries appeared normal. A bilateral cornual resection was performed.<sup>12</sup> The right parovarian cyst was punctured.

*Pathologic Report.*—(Dr. Plaut.)

*Microscopic:*

*Right Cornu.*—Adenomyosis of tubal angle. The glandular structures themselves are not inflamed. In the adjoining muscle tissue slight perivascular accumulations of round cells are noted.

*Left Cornu.*—Midportion of tube in cross section and oblique section. The folds in places are somewhat thick but there is no inflammation.

*Diagnosis.*—Adenomyosis of tubal angle.

Culture (Dr. Seligmann) of the cornual portions of the tubes was reported as being positive for *Salmonella typhi murium* in pure growth. Subsequent cultures of the feces were reported as being negative for this organism. Agglutination tests done immediately upon report of the culture were negative in a dilution of 1:40. One week later the agglutination test was positive in a dilution of 1:80.

### Discussion

The method by which these organisms infect the tubes and ovaries is of some interest but cannot be stated with certainty at this time.

1. Infection via the blood stream is believed to be the usual route whereby localized septic metastasis such as osteomyelitis, empyema, etc., is usually produced. In such septic infections a positive blood culture may be frequently obtained. *Salmonella* organisms have been cultured from the blood in postabortal and puerperal sepsis, in infected myomas and in infected hematocele. Unfortunately there is no instance of positive blood cultures reported in any case of *Salmonella* salpingo-oophoritis, although by analogy it would seem that the infection is probably hematogenous.

2. Ascending infection from the vagina and uterus. In the three cases of *Salmonella* infection of the tubes reported in the literature, it

is of interest that none showed *Salmonella* infection in the culture of the feces. Of the two cases herein reported, in one the stool was positive for *Salmonella typhi murium*, which is the first time that this finding has been observed. It is believed that the rectal pus was secondary to minute or incomplete perforation of the ovarian abscess into the rectum.

3. Infection of the tubes and ovaries by direct extension from the intestines. Such infection to a normal tube and ovary from the intestine seems improbable. However, it is well known that secondary invasion by intestinal organisms to a pyosalpinx or tubo-ovarian abscess in adherent tubes and ovaries may occur.

4. Other sources of vaginal infection (prostatic secretion, salivary contamination, etc.) have not yet been demonstrated although such a possibility cannot be denied at the present time.

In Case 1, the presence of extracellular gram-negative diplococci in the smear of the ovarian pus recovered at operation, suggests the possibility of a preceding gonorrheal salpingo-oophoritis. In Case 2, the occurrence of pelvic infection subsequent to divorce is clinically suggestive of gonorrheal salpingitis, but there are no laboratory findings to confirm this possibility. However, it seems likely, but unproved, that in both cases the tubes had been the seat of a previous infection, and constituted a locus minoris resistentiae to subsequent infection with the *Salmonella* organism. Whatever the method of inoculation, the positive agglutination tests in both cases herein reported as well as in the three cases previously reported, definitely indicate that this organism is not a contaminant.

It would appear that in many infections of the tube and ovary in which gram-negative bacilli are found and which heretofore have been considered to be coli infections may prove to be of *Salmonella* origin.

Until our second case was found to be of *Salmonella* infection on routine bacteriologic study, it was believed that the clinical course of *Salmonella* salpingitis was characterized by a prolonged febrile illness which did not respond to the usual therapy instituted for pelvic infection. It has been repeatedly observed that in a patient with pyosalpinx, the temperature will drop to normal within three weeks following the institution of bed-care and supportive treatment. Ovarian abscesses may not respond as quickly, but also tend to subside although the period of time is more prolonged. However, in Case 2 there is no evidence of protracted illness, in fact, the infection was obviously inactive on admission. Notwithstanding, it would seem that the possibility of *Salmonella* infection should be considered in patients with pelvic infection who are refractory to the ordinary methods of therapy.

The treatment of *Salmonella* infection of the tube would not seem to differ from that of tubal infections caused by other organisms. This has been described in detail elsewhere.<sup>13</sup> Although no generalization



can be drawn from so few cases, whether the treatment is radical, as in Case 1, or extremely conservative, as in Case 2, the end results have been satisfactory.

### Summary

1. Two cases of Salmonella infection of the tubes and/or ovaries are reported. Three additional cases were found in the literature.
2. In one of the two cases presented, a positive stool culture of Salmonella is reported for the first time.
3. The route of infection has not been definitely ascertained, although blood stream infection (possibly to previously infected tubes) is not unlikely.
4. The positive agglutination tests indicate that the Salmonella bacilli are of etiologic significance in the causation of pelvic infection and are not accidental contaminants.
5. The manifestations of such infections are not clinically distinctive. Certain identification can be made only by bacteriologic and immunologic methods.
6. The treatment would not seem to differ from that of salpingitis caused by other bacterial organisms such as the gonococci.

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## THE UTERINE MOTILITY ASSOCIATED WITH POSTERIOR POSITIONS OF THE OCCIPUT

### Observations Made With the Lóránd Tocograph

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THE reason why the occiput presents in the posterior position is not known. And why, when such presentations occur, engagement fails to take place, or, after it has occurred the occiput fails to rotate anteriorly, are sometimes questions which are difficult to answer, especially while labor is in progress.

Lack of satisfactory answers to these questions raised the additional question as to whether greater knowledge of the uterine contractions might aid in the solution of some of them.

With these thoughts in mind, we re-examined our tracings of uterine motility, secured with the assistance of a Lóránd tocograph,<sup>1, 2</sup> either before or during the labors, of patients whose infants happened to present with their occiputs in the posterior position.

### Results

Women delivered in the hospital of the University of Pennsylvania between Jan. 1, 1938, and Dec. 31, 1942, acted as subjects. Table I summarizes the number of observations.

### Uterine Motility During Pregnancy

*Relation of Uterine Motility to Position of Occiput on Engagement.*—The uterine activity of 26 of the 55 patients (Table I) was registered before the onset of labor. The variety of the contraction patterns secured at this time was not unusual. It is concluded, therefore, that the character of the uterine activity, present prior to the onset of labor in all probability, had nothing to do with the position in which the occiput happened to present.

TABLE I. PATIENTS EXPERIENCING POSTERIOR PRESENTATIONS OF THE OCCIPUT

	PATIENTS
Occiput posterior presentations	55
Failure of the head to engage followed by cesarean section	5
Outlet dystocia followed by cesarean section	2
Delivered occiput anterior	20
Delivered occiput posterior	28
Tracings before delivery	26
Tracings during labor	28

### Uterine Motility During Labor

*Failure of Head to Engage.*—Five of the 55 patients (Table I) failed to engage the heads of their infants and were delivered by the ab-

dominal route. The pelves of these women were normal in size and configuration. The smallest of the 5 infants weighed 3,720 grams, the average for the group being 4,117 grams. Four of the 5 mothers were traced during labor and all registered a satisfactory uterine motility. These observations suggest that the size of the infant was the important factor in the failure of engagement.

The heads of 2 infants engaged but outlet contractions prevented vaginal deliveries; both women experienced normal uterine motility.

*Direction of Rotation of the Occiput.*—Twenty-three patients supplied tracings made during labor and were delivered vaginally. Their pelves were normal in size. Their infants varied in weight from 1,330 to 4,720 grams with an average of 3,377.

The relation between the quality of the uterine motility of these 23 patients, as revealed by the tocograph, and the direction of rotation of the fetal occiput are indicated in Table II. Of 11 patients who registered a satisfactory motility, 4 rotated the occiput to the anterior position, and of 12 who experienced poor motility, 4 also did so. This observation suggests that the successful rotation of the occiput to the anterior position did not depend upon the quality of the uterine contractions.

TABLE II. INFLUENCE OF QUALITY OF UTERINE MOTILITY UPON ROTATION OF OCCIPUT ENGAGING IN THE POSTERIOR POSITION

MOTILITY	PATIENTS		
	NUMBER	ROTATION	
		ANTERIOR	POSTERIOR
Good	11	4	7
Poor	12	4	8

The 11 infants whose occiputs rotated anteriorly weighed 3,476 grams on the average, and the 12 infants whose occiputs rotated posteriorly weighed 3,380 grams. The closeness of these two averages suggests that infant size did not influence the direction of rotation of the occiput, especially in view of the fact that the large infants rotated in both directions.

Since the quality of the uterine motility and the size of the infant did not appear to influence the direction of the rotation of the occiput, it would seem reasonable to infer that the direction of rotation was influenced chiefly by some other factor. The majority of the patients were not x-rayed, so for that reason we have no information which might throw light upon the influence of pelvic shape upon the direction of rotation of the occiput.

*Contraction Pattern.*—The patients exhibited a variety of contraction patterns during labor, but no one type of pattern predominated.

The patterns permitted themselves of classification in three categories: (a) normal motility, (b) primary inertia and (c) disproportion, examples of which are described below.

*Normal Motility.*—Normal motility is illustrated by the tracings reproduced in Fig. 1.

The patient, M. J., had had one previous pregnancy. Her pelvis was of normal size. The labor lasted 23 hours, and her contraction pattern was normal when registered on several occasions. The second stage of labor lasted only 1½ hours, yet the infant weighed 3,760 grams. The occiput delivered in the posterior position. Tracing (a), Fig. 1,

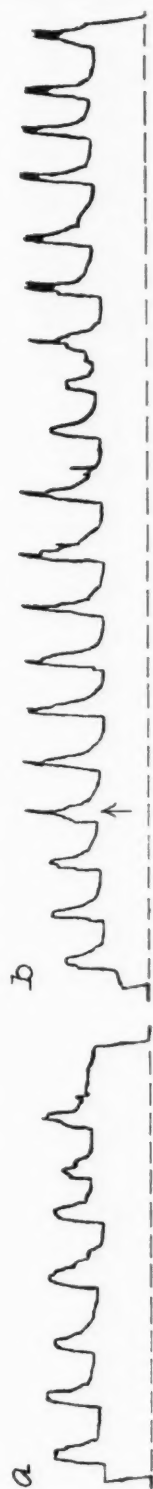


Fig. 1.—Patient M. F. Tracing (a) was recorded when the cervix was dilated 2 cm. Both the tonus and the contractions are normal. Tracing (b) was made late in the second stage of labor. The tonus and contractions are normal. Voluntary contractions of abdominal muscles start at arrow, and are indicated by "steeples" at crests of waves produced by the involuntary contractions. Both tracings are typical of normal motility during labor.

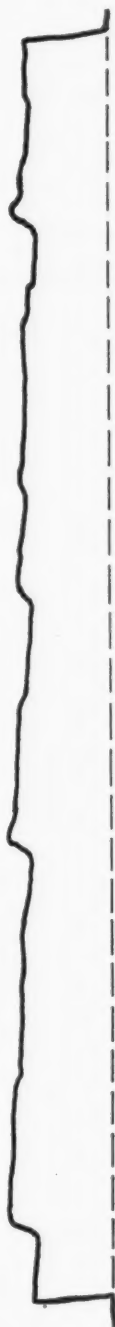


Fig. 2.—Patient V. C. Tracing recorded as cervix was beginning to dilate. The tonus is normal, but the contractions are weak. This tracing is typical of "normotonic" inertia.

was secured when the cervix was dilated 2 cm., and tracing (b) when the patient was ready for delivery. The wave at the arrow presents a "church steeple" at its crest. This results from the contractions of the abdominal muscles at the height of the involuntary uterine contractions. Both tracings reveal an average uterine tonus and contractions of average character and magnitude.

*Primary Inertia.*—This condition is illustrated in Fig. 2. The patient, V. C., was a primipara with a normal pelvis. Her labor lasted 53 hours, with a second stage of  $5\frac{3}{4}$  hours. Clinically her contractions were of poor quality throughout labor. The tracing shown in Fig. 2 was made just as the cervix was beginning to dilate, which was 41 hours after the onset of painful contractions, and only 12 hours before delivery. The infant weighed only 2,880 grams. The tracing shows that the patient was experiencing a normal tonus but her contraction waves were of unusually small magnitude. Inertia is indicated by the small size of the waves; and the presence of a normal tonus makes it possible to classify the inertia as being of the "normotonic" variety.<sup>3</sup>

*Disproportion.*—During a labor not complicated by the development of a disproportion, the uterus may or may not experience any progressive increase in tonus, but if it does, the increase usually is moderate in degree, even during the late second stage.

In the presence of normal contractions, disproportion affects the uterine motility by increasing the tonus of the uterus, which change is recorded readily by the tocograph. An example is reproduced in Fig. 3. The patient, E. R., was a primipara with a normal pelvis. Her labor lasted only 14 hours, but the second stage consumed 5 hours of it. She was delivered of a 4,150 gram infant at the outlet by forceps. Tracing (a), Fig. 3, was made when the cervix was dilated 2 cm. and before evidence of disproportion had developed. This tracing reveals a normal tonus and contraction waves of normal character and magnitude. Tracing (b) was made late in the second stage of labor and reveals evidence of disproportion. This tracing shows contractions of normal magnitude but an unusually high tonus, which is measured in terms of the distance of the wave troughs above the base line seen at the ends of the tracing.

### Comment

The number of patients forming the basis for this study is small, but it was unselected except for the fact that each patient happened to have her uterine motility recorded either before or during labor.

No tocographic observations are available to indicate the relative frequency with which unsatisfactory uterine motility accompanies labors not complicated by posterior positions of the occiput. Therefore, it cannot be stated with certainty whether the present patients experienced labors which were of unusually poor quality. The impressions have been gained, however, that the incidence of poor motility in these patients was not greater than the average, and that their contraction patterns in general were not of unusual character. In other words, it appears that posterior positions of the occiput are not necessarily accompanied by unsatisfactory uterine motility.





Fig. 3.—Patient E. R. Tracing (a) was made when the cervix was dilated 3 cm. The tonus and contractions are normal. Tracing (b) was registered late in second stage of labor. The contractions are normal, but the tonus greatly increased. An unusual increase in tonus is evidence of disproportion.

This study emphasizes several facts. The anterior rotation of a posterior occiput does not depend upon the quality, i.e., strength of the uterine contractions, or upon the size of the infant. If this is true the configuration of the pelvis in all probability plays the important role in directing the rotation of the occiput.

A second observation concerns the effect of disproportion upon uterine tonus when uterine motility is normal. The finding of a marked increase in tonus during labor should suggest to the obstetrician that he is dealing with a definite disproportion and, therefore, that he should be guided in his conduct of the patient's labor by this finding.

### Summary and Conclusions

1. Posterior positions of the occiput may be associated with either a good or a poor motility, and there appears to be no unusual tendency for the latter to occur.
2. The character of the motility before the onset of labor does not appear to determine the position of the occiput on engagement.
3. Disproportion is a more important cause of failure of engagement of a posterior occiput than is poor motility.
4. Poor motility is not the important factor in determining the direction of rotation of an occiput which engages in the posterior position.
5. In the presence of normal uterine contractions, disproportion results in an abnormal increase in uterine tonus.

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## THE VOORHEES BAG\*

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IN AN effort to evaluate the merits of the Voorhees bag we have reviewed our records for the 5½-year-period from January 1, 1938, to July 1, 1943. In this time there were 17,701 deliveries at the Elizabeth Steel Magee Hospital. The Voorhees bag was used 41 times for the following indications and with the enumerated results:

CASES	INDICATIONS FOR USE	FETAL DEATHS	MATERNAL MORBIDITY
9	Induction of labor	7	1
2	Placenta previa	2	1
3	Placenta ablatio	3	0
6	Fetal distress, due to cord complications	2	1
19	Inertial labor	5	6 1 Maternal death
2	Abnormal presentations	1	0

The 20 fetal deaths on analysis show that 2 infants were nonviable, weighing 970 and 1,300 grams; 1 was an anencephalic; 2 were hydrocephalics; on one other infant craniotomy was performed; 4 infants were premature, weighing less than 2,500 grams. In all instances the pregnancies were complicated by placental abnormalities or toxemias; 2 infants definitely and 3 probably had intracranial hemorrhages resulting from difficult deliveries. In 2 cases the cords were prolapsed on admission and in a third the cord prolapsed after a small bag used for induction was expelled; 1 infant died during labor and was macerated at birth; 1 infant probably died as the result of a severe nephritic toxemia in the mother.

Whether the Voorhees bag has a place in modern obstetrics is questioned by many. In recent years its use has undoubtedly decreased and in some centers has been eliminated. We are of the opinion that it still has its place in the obstetric armamentarium but only under certain conditions and for certain specific purposes.

The classic primary indications for the Voorhees bag as stated in the textbooks are: (1) to prevent bleeding, (2) to induce labor, and (3) to dilate or complete the dilatation of the cervix.

We feel that in marginal placenta previa, or in partial placenta previa in multiparas in which delivery by the vaginal route can be carried out, simple rupture of the membranes is easier, safer, and more efficient than introducing a bag. The cervix and lower uterine segment

\*Read at a meeting of the Pittsburgh Obstetrical and Gynecological Society, October 11, 1943.

in these cases is too friable to warrant any undue manipulation which might cause deep lacerations and hemorrhage. In the two cases in which a bag was introduced for placenta previa, the fetal mortality was 100 per cent, although heart sounds had been present. In one of these two cases a craniotomy was necessary to avoid lacerating the cervix, as too small a bag was introduced and dilatation was inadequate for delivery. The other infant was slightly premature, weighing 2,450 grams. In both, the bleeding was controlled until the bag came out, at which time hemorrhage recurred.

In placenta ablatio we find no use for the bag. The principle of treatment for this pathology, when vaginal delivery is to be undertaken, is to keep the uterus contracted, thus closing off uterine sinuses. A bag increases the size of the uterus, while simple rupture of the membranes with evacuation of all possible fluid accomplishes the desired decrease in size. When pitocin is also given the uterus is kept rather constantly contracted and the termination of labor is expedited. Here again, with the bag, the fetal mortality was 100 per cent, but two infants were premature and the heart sounds were absent in one case at insertion of the bag. The third infant was an anencephalic. Profuse hemorrhage occurred from the fetal head. The Voorhees bag was inserted to speed delivery as the hemorrhage was thought due to a partial separation of the placenta.

As to the second primary indication, i.e., to induce labor, we are not in favor of the use of the bag, except in certain rare instances; one of which would be the presence of a hydrocephalic infant. If the head is in the pelvis, the cervix partially effaced and slightly dilated, and no cephalopelvic disproportion existent, rupture of the membranes, followed by pitocin in small doses, is, we believe, the method of choice. If the cervix is not "ripe" for rupture of the membranes, a complete medical induction will usually prepare it to meet the above requirements. In nine patients labor was induced by insertion of a bag. Six had toxemia. One fetus was dead; one was definitely postmature, and one was a hydrocephalic monster. Only two infants survived; mortality 78 per cent. Fetal heart sounds were absent in only two of the toxemic cases prior to insertion of the bag and these babies were premature, one being nonviable. One of the infants died 48 hours post partum from intracranial hemorrhage.

We believe that the third primary indication, namely, to complete the dilatation of the cervix, is the soundest indication for the use of the Voorhees bag. In many of these instances the Waters type extra-peritoneal cesarean section has been advocated. We, however, feel that this operation should be reserved for those cases in which cephalopelvic disproportion exists and is complicated by mild or moderate infection. The degree of potential or actual infection present in a uterus is exceedingly difficult to evaluate. If one places an incision in a definitely infected uterus, that incision will invariably become necrotic and will

form a focus in which organisms continue to multiply, thereby increasing the hazard to the patient. In frankly infected cases even in the absence of cephalopelvic disproportion, the Porro type section is the procedure of choice. In potentially infected cases without cephalopelvic disproportion, we feel that an intact uterus is a safer uterus, and the Voorhees bag has a definite place in handling this type of pathology. Besides absence of cephalopelvic disproportion one of the following pathological conditions should exist:

- (1) Malpresentation, such as a face, transverse, or double footling.
- (2) Dystocia due to anomalies of expulsive forces or due to cervical pathology with cessation of progress for a reasonable period after labor is established. By progress we mean descent, or increasing effacement or dilatation of the cervix.
- (3) Some threatening complication which necessitates rapid delivery such as a fulminating toxemia, amnionitis, or prolonged rupture of the membranes.
- (4) Some evidence of fetal distress or a prolapsed cord with a viable baby.

There were 27 cases in this group, divided as follows:

	CASES	FETAL DEATH
Prolapsed cord	2	1 (Prolapsed cord on admission)
Fetal distress due to cord interference	4	1
Faulty presentation (transverse, face)	2	1 (Prolapsed arm and cord on admission)
Uterine inertia	19	5

The gross fetal mortality was 29.6 per cent and the corrected fetal mortality 18.5 per cent. Three infants were premature but all survived.

In the 19 cases of uterine inertia, the average length of labor was 48½ hours. The average length of time the bag was in place was 71½ hours, 20 hours being the longest period. There were 5 fetal deaths. One was a hydrocephalic, necessitating craniotomy. In 3 other cases (2 primigravidas) there was a relative cephalopelvic disproportion resulting in "considerable difficulty" at delivery and obvious intracranial hemorrhage in one infant. Two of these were breech presentations. The cervix was completely dilated by the bag before delivery was attempted. The fifth fetal death was also a breech presentation, in which the bag was removed after 11 hours, with the cervix dilated only 7 or 8 cm. The fetal heart sounds had disappeared. Delivery was accomplished 11 hours later. The 1 maternal death of the series occurred in this group. This patient was a 20-year-old, emaciated, anemic, gravida v, who went into labor at 8 months, after having been in the hospital 4 days for observation. As the cervix was dilated only 3 cm. after 17 hours of labor, a number 4 Voorhees bag was inserted. This was expelled in 4½ hours, following which delivery by version and extraction was performed through an incompletely dilated cervix. A cervical laceration extending into the broad ligament resulted, with hemorrhage and death a few hours later despite hysterectomy. Besides this



case there were five others in which too small a bag was introduced to permit delivery following its expulsion without further measures. These "further measures" were manual dilatation of the cervix, Dührssen's incisions, craniotomy, Braxton-Hicks' version and a two-day delay after which version was performed.

In two instances the bag was unsuccessful: (1) Following insertion of the bag the fetal heart sounds slowed down so markedly that the bag was removed within 15 minutes of its insertion. The infant was stillborn. (2) A large enough bag after being in place 11 hours only dilated the cervix to 7 or 8 cm.

To get satisfactory results with a Voorhees bag we feel that the patient should be in labor and the membranes should preferably be ruptured. The presence of a contraction ring is no real contraindication, for the displacement of the presenting part by the bag tends to overcome this resistance so that delivery can occur or be accomplished.

Our technique for insertion and removal of the Voorhees bag is as follows:

The patient is given an anesthetic and usually by palpation or occasionally by vision, a carefully folded bag is introduced through the cervix. The cervix must be dilated at least 2 cm. or easily dilatable to this point. We feel that a number 5 or 6 bag should be used, preferably the latter. Most of our failures and the one maternal death in this series can be attributed directly to using too small a bag and securing only incomplete dilatation of the cervix, necessitating manual dilatation or incisions to effect delivery. The bag is filled with sterile water, a bandage is attached to the stem and is brought between the patient's legs and over a pulley at the foot of the bed. A weight is attached. We usually use one pound and do not hesitate to increase it to two. Rectal examinations are performed as necessary. When the bag is about to slip through the cervix the patient is put on the delivery table and draped. An anesthetic is administered and only when the patient is anesthetized is the water released and the bag removed. Version and extraction is carried out in most instances.

We realize that the bag has obvious disadvantages, namely, the need of anesthesia for insertion, operative delivery, and possibility of infection. Nine of the 41 patients in this series had a temperature of 100.4° F., or over for two or more consecutive days following delivery, excluding the first 24 hours. One must remember, however, that when the Voorhees bag is employed, the case is a complicated one and the operator is in trouble.

### Conclusions

1. In the absence of cephalopelvic disproportion, the Voorhees bag has a definite place in modern obstetrics.
2. Placenta previa, placenta ablatio, and induction of labor are not primary indications for its use.

3. Its chief use is to complete the dilatation of the cervix, in cases of inertial labor, when progress has ceased; when there is fetal distress from cord interference, or when the cord is prolapsed and the baby viable; when there is an abnormal presentation, or when delivery must be hastened due to a threatening maternal complication.

4. It should be used according to a set technique; a large enough bag should be employed to dilate the cervix adequately, and it should not be removed until the patient is anesthetized and ready for delivery. The delivery should immediately follow in most instances.

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**Ramos, A. P., Albertelli, J. F., and Colombo, E.: The Value of Quantitative Determination of Gonadotropin in the Diagnosis of Chorionepithelioma, Rev. argent. de cien. med. 1: 8, 1943.**

The authors state that the maximum guarantees of early diagnosis of chorionepithelioma are to be found through biologic tests. Since this neoplasm always secretes huge amounts of choriogonadotropins, the quantitative determination of these by-products, in the absence of pregnancy, is of utmost diagnostic importance. For diagnosis the presence of at least 50,000 rat units per liter are required.

The authors conclude that the existence of large amounts of gonadotropin is not essential if re-examinations of urine reveal an ascending curve following an abortion caused by a mole, or if a degeneration of the trophoblast is suspected. They carry out weekly estimates for at least two months, searching for 200 units. If this quantitative determination increases gradually to 500 or 1,000 units per liter the diagnosis can be established and treatment be instituted.

Two outstanding cases which were followed by hysterectomy and pathologic substantiation of the tumor are mentioned in this article.

CLAIR E. FOLSOME.

**Matters, R. F.: Sulphonamides and Purulent Peritonitis, M. J. Australia 2: 85, 1943.**

The author found that intraperitoneal sulfanilamide has proved most effective in cases in which the peritoneum has been infected. It is rapidly absorbed from the peritoneum within 24 hours. The gross pus must be removed before the powdered sulfanilamide is applied. The sulfanilamide does not appear to affect the healing of wounds or the normal state of the intestines.

WILLIAM BERMAN.

## MANAGEMENT OF THE CLIMACTERIC WITH ETHINYL ESTRADIOL\*

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THE climacteric is a syndrome composed of hot flashes, vertigo, irritability, moods of depression, tendencies toward obesity and toward hypertension, premenstrual tension, increased frequency of headaches, and insomnia. Less frequently, leucorrhea, arthralgia, and palpitation of the heart are observed. In varying degrees of severity this syndrome has been noted in most women by the age of fifty. The largest number of healthy climacteric women are but slightly affected. There are, however, gradations in severity such that a significant proportion are notably distressed by this pattern of symptoms. Efficiency appears to be decreased in the most severely affected. The object of this study is to determine the effect of ethinyl estradiol on the climacteric women as evaluated by available objective and subjective criteria.

Prior to the introduction of estrogen for the management of the severe climacteric syndrome, sedatives, tonics, thyroid and psychotherapy have been utilized. The success of these measures has been notably limited, and during the past five years estrogen administration has become the treatment of choice for the severe case. Oral administration was initially achieved by a nonphysiological estrogenic preparation, diethylstilbestrol. In the effective dose range this preparation produced nausea in a sufficient number to invalidate its general employment.

Inhoffen and Hohlweg<sup>1</sup> prepared ethinyl estradiol by means of altering the seventeenth carbon atom in such a manner as to produce a substance approximately fifteen times as active as estradiol, when given by mouth. Proliferative changes in the endometrium were observed by Clauberg and Ustun<sup>2</sup> following a dose of 56 mg. of this preparation which was given over a period of twenty days. Subsequently, Salmon and his associates<sup>3</sup> administered this substance to patients who had climacteric symptoms, which resulted in marked relief. These workers noted that with relatively large doses the vaginal mucosa underwent changes typical of estrogenic stimulation. Moreover, there were some instances of abdominal pain, malaise, chills, vertigo, nausea and vomiting, even though enteric coated tablets were used. It was interesting to observe that when the preparation was dissolved in alcohol all of the patients reported disagreeable side effects.

\*Ethinyl estradiol tablets were donated by Schering Corporation. This study was aided by the Christine Breon Fund for Medical Investigation.

Ethinylated estradiol has been found to be effective following oral administration.<sup>4-6</sup> The required dose has been determined to be quite small. The active portion apparently is slowly released from its ester, thus a continued effect is maintained.

### Procedure

Unselected consecutive clinic patients who presented the symptoms and physical findings of the climacteric syndrome have been investigated by means of basal body temperature determinations, vaginal hydrogen ion concentration readings, and ordinarily endometrial biopsies. When the patient continued to menstruate, the biopsy was taken during the fourth week of the cycle. Detailed subjective reports were recorded for one control cycle, following which the patients were given 50 microgram ethinyl estradiol tablets daily by mouth for courses of twenty-one days. Then there is an interval free from treatment.<sup>7</sup> This free interval usually lasts for one week. Its purpose is to permit the regression of the endometrium and possibly to allow the estrin sensitive tissues to be restored to their optimal effectiveness. Moreover, during this interval, cyclic bleeding can occur. Half of the women found the seven-day interval too long since before it had been completed there was a recurrence of hot flashes. Occasionally one of these who failed to satisfactorily carry through this seven-day interval without estrogen, was given additional tablets in such a manner that the therapeutic plan provided twenty-four days of treatment, then followed a four-day interval without treatment. A modified human assay method along the line suggested by Freed<sup>8</sup> was carried out. In the well-advanced climacteric, bleeding was infrequently seen, in which cases it was customarily scant in amount. In late climacteric cases, bleeding is not desirable. Because of this, the dose of ethinyl estradiol was occasionally lowered to a subthreshold level which was still effective in preventing the vasomotor disturbances.

### Observations

Forty-five women with an average age of forty-six (range thirty-eight to fifty-four) who complained of hot flashes and other climacteric symptoms for an average of 3 years, have been studied prior to treatment for a control cycle, and then through a number of estrogen treated cycles. These varied from three to twenty-four per patient. Three hundred forty-eight treatment cycles compose the basis for this study. Control cycles showed evidence of ovulation in but eight, or 17 per cent of the patients although approximately 55 per cent of the women continued to menstruate. Evaluation of ovulation for the control cycles was made by endometrial biopsies and basal body temperatures in twenty-six patients, and in nineteen by basal body temperatures alone. Of the fifty-five per cent of the patients who continued to menstruate, there was some degree of progestational change in the endometrium during the last half of the control cycles in 17 per cent. The remaining endometrial biopsies showed healthy endometrium with varying degrees of proliferation. The patients had an additional biopsy on completion of six months of treatment. None of these have shown hyperplasia of the endometrium developed during the period of investigation.

Study of the control cycles showed fluctuations in the frequency of the syndrome symptoms at various times, some of them not associated with ascertainable stimuli. The variability between patients also was relatively wide in the objective as well as the subjective standards for the syndrome.

The symptoms and findings before and after treatment with minimal doses of ethinyl estradiol are summarized in numerical form in Table I.

TABLE I. FREQUENCY OF CLIMACTERIC SYMPTOMS IN FORTY-FIVE CASES PRIOR TO AND FOLLOWING ETHINYL ESTRADIOL TREATMENT

SYMPTOMS	BEFORE TREATMENT		FOLLOWING TREATMENT	
	NUMBER	PER CENT	NUMBER	PER CENT
Flashes	45	100	1	2.2
Sweating	42	93	1	2.2
Irritability	40	89	3	6.6
Insomnia	34	76	2	4.4
Vertigo	31	69	2	4.4
Depression	30	66	0	0
Obesity trend	24	53	-	-
Headaches	22	49	4	9.1
Mild hypertension	20	44	-	-
Menstrual irregularity	12	27	2	4.4
Palpitation	11	24	0	0
Leucorrhea	10	22	3	6.6
Arthralgia	10	22	0	0
Nausea	1	2	5	11.

Nine per cent had headaches persist after this minimal treatment. This is in accord with the finding of Groper.<sup>4</sup> Nearly seven per cent had nervousness and restlessness after treatment although the flashes were well controlled. Approximately two per cent of the patients continued to have flashes, although these were decreased in severity and frequency. Attempts to decrease the dosage to 20, 30, or 40 milligrams of ethinyl estradiol daily resulted in the reappearance of flashes in most patients who had been controlled with 50 milligrams. In patients who were accustomed to the occasional use of alcohol it was found that flashes ordinarily appeared the day following its use even though they had taken their customary dose of estrogen. However, doubling the dose as a prophylactic measure on these occasions, tended to restrict the flashes completely.

TABLE II. EVALUATION OF RESPONSE TO 0.00005 GM. ETHINYL ESTRADIOL DAILY

	AVERAGE
1. Age at onset of flashes	46 years
2. Duration of flashes at onset of treatment	3 years
3. Duration of cyclic bleeding following treatment	5.0 days
4. Disappearance of flashes after start of treatment	3.8 days
5. Onset of flashes following cessation of treatment	5.5 days

In this series, as shown in Table II, the average duration of treatment prior to control of the flashes was 3.8 days, while in subsequent cycles the average was decreased to three days. Residual partial saturation with the estradiol might account for this decrease. Upon completion of a 21-day course of estrogen tablets, it was noted that an average of 5.5 days (range one to twelve days) passed before the patient reported recurrence of the flashes.



The hydrogen ion concentration of the midvagina was estimated colorimetrically prior to therapy. The average reading was 5.3, whereas following three weeks of continuous treatment with ethinyl estradiol, the average reading decreased to 4.9. The ranges were 4.8 to 5.8 before treatment and 4.4 to 5.2 after treatment. However, many patients showed negligible change in pH even when the flashes were prevented as a result of the estrogen treatment.

Bleeding under the influence of ethinyl estradiol therapy has lasted somewhat longer than in the nontreated individual. The range varied from no bleeding days to durations of six days. One purpose of the cyclic use of estrogen has been to allow a free interval during which time menstruation may occur. Ethinyl estradiol in the small dose used in this study does not ordinarily cause withdrawal bleeding in women past the menopause, and yet it is effective in suppressing the distressing vasomotor and emotional symptoms. In the menstruating group which included more than half of this series, bleeding during the treatment phase or during the week free from treatment, was not excessive on the dosage employed. There were varying degrees of regularity but no instances of well-defined menorrhagia or metrorrhagia.

While employing a dose of 0.05 mg. of ethinyl estradiol orally each day for three weeks, there has been an incidence of nausea in 11 per cent of the patients. This has been minimal and transitory. There appears to be an increase in nausea with increased doses of this hormone.

Patients having some degree of hypertension seem to have greater unpleasant reactions from their climacteric or after estrogen withdrawal, than do the remaining patients. An arbitrary level of 140/90 under approximately basal conditions, on two occasions, has been accepted as the criteria of hypertension in this study.

### Discussion

Patients having unequivocal climacteric syndromes, such as those following surgical castration, tend to reach an equilibrium after many months without treatment. When ethinyl estradiol has been administered to these individuals, however, there seems to be less severe distress than otherwise obtained during the stabilization period. Control of vertigo, hot flashes, sweating, headaches, the tendency toward hypertension, and a tendency toward obesity, together with irritability, leucorrhea, insomnia, fatigability, numbness of extremities, and menstrual irregularity appeared to be achieved by means of quite small doses of this estrogen. The general condition and subjective feeling of fitness was reported by nearly every patient.

The average vaginal pH changes during ethinyl therapy seemed to have significance in evaluating estrogenation as determined by the colorimetric method. Although inconstant, they were of the order of magnitude of the normal cyclic variation. There was a decrease of an average of 0.4 in the midvaginal secretion observed during treatment with this preparation. However, the hydrogen ion concentration seemed to be less sensitive than the subjective vasomotor reactions in estimating the response to the hormone treatment.

Control of the distressing vasomotor and emotional symptoms of the climacteric has been obtained with this orally active and relatively well-tolerated estrogen. Minimal doses have been effective and side reactions few, none of them of severe degree. Probably the paucity of extraneous reactions is a function of the small dose employed, for when it was increased appreciably the number and incidence of reactions was greater.

### Summary

The climacteric syndrome has been effectively managed in 45 patients through 348 cycles, by means of ethinyl estradiol treatment. This was given in the orally active enteric-coated 50 microgram tablets daily for twenty-one days, followed by a withholding interval of a week's duration. Following six such cyclic treatments, the estrogen was again withheld, this time for a period of one month, and evaluation of the various components of the syndrome was made. Continuation of the therapy was usually indicated. It was not determined whether such estrogen treatment hastens, postpones, or has no effect on eventual symptomatic equilibrium. Transitory sequellae of mild degree occurred at some time during estrogen treatment in 11 per cent of the 45 consecutive patients.

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## ROUTINE ORDER OF EXAMINATIONS FOR THE DIAGNOSIS OF STERILITY

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ONE of the greatest obstacles to the comprehensive analysis of sterility in private practice is the time required by the physician in making the necessary examinations and the consequent prohibitive cost to the patient. Abbreviated diagnostic studies or empiric treatments are as a whole economically, as well as scientifically unsound, and furnish no satisfactory short cut to a comprehensive and well-founded sterility diagnosis. Patients are frequently encountered in private practice who have spent as much as \$200 to \$1,500 for various treatments for sterility without a semblance of a diagnostic study such as here outlined. It seems rather inexcusable. A diagnostic agenda may be considerably simplified by grouping the various examinations in a sequence that is most advantageous both from the diagnostic point of view and the time consumed. To accomplish this, it is necessary that the basic diagnostic examinations of both partners shall be conducted together, in a manner that one complements the other. If not, the picture is apt to be too incomplete to form a basis for a sound diagnosis and prognosis.

The tabulation which follows lists the various examinations in the order ordinarily conducted. References are given to various special technical procedures involved. The entire diagnostic workup requires a single visit by the husband and four visits by the wife. These four visits are usually scattered over a period of three or four months, partly because of therapeutic considerations and partly because examinations and records over a period of several months usually form a much better basis for a diagnosis and prognosis than is possible with a more abbreviated study.

Economies in the time required for the examinations are introduced whenever possible. For Section II, the husband and wife are given a morning appointment for the same day, thus permitting all the laboratory work of this section for both partners to be gotten under way or completed in a single morning. A single sample of blood, some of which is oxalated, permits a complete blood examination, sedimentation rate, corpuscular volume, Wassermann, determination of Rh factor or other tests with the expenditure of only 3 or 4 minutes' time outside the laboratory work. The urine is examined while the patient is resting for the basal metabolic rate and if there is any sugar in the urine, part of the blood sample may be used for a fasting blood sugar determination.

It is usually best to make no pelvic examination at the time of the general medical survey, but rather to defer this to appointments when

TABLE I. TYPE OF EXAMINATIONS FOR STERILITY AND ORDER OF CONDUCT\*

SECTION I. Bottle specimen of semen brought to office by patient first month of diagnostic survey. Patient's presence in office not required.

Observations on semen:<sup>1-6, 8</sup>

1. Amount and physical characteristics.
2. Motility and degree of motility.
3. Density of spermatozoa (number of spermia per cu. mm.).
4. Differential. Type and ratio of pathologic spermatozoa.

\*In individual cases, special circumstances may make it advisable to alter the order given here, but it is usually best to complete any section in its entirety if any of the tests in it are to be done.

SECTION II. Visit by both husband and wife.

Time of examinations—first month of diagnostic survey.

Husband:

Length of office visit—3 hours.

1. Urine examination.
2. Basal metabolic rate.<sup>1, 5, 7</sup>
3. Complete blood examination.
4. Blood for Wassermann test.
5. Blood for Rh factor determination if history of miscarriages.<sup>9</sup>
6. Anamnesis.<sup>10</sup>
7. General physical examination.<sup>10</sup>
8. Examination of prostatic smear, including Gram stain.<sup>1, 5</sup>

Wife:

Length of office visit—3 hours.

1. Urine examination.
2. Basal metabolic rate.<sup>1, 5, 7</sup>
3. Complete blood examination, including sedimentation rate if history of pelvic inflammatory disease or of any chronic infection.
4. Blood for Wassermann test.
5. Blood for determination of Rh factor and anti-Rh factor if history of miscarriages.<sup>9</sup>
6. Anamnesis.<sup>10</sup>
7. General physical examination (without pelvic examination).
8. Instruction on ovulation timing, basal body temperatures, vaginal smears,\* and other means by which the time of ovulation may be determined. This includes the making of proper graphs or charts.<sup>1, 7, 11, 12, 13, 14, 15</sup>
9. Discussion of the general principles of the treatment of sterility and of the routine handling of the sterility problem.

\*Patient is instructed to take smears on the sixth, twelfth, and twenty-second day of cycle and day of thermal shift, or at other appropriate intervals.

SECTION III. Visit by wife.

Length of office visit—30 to 40 minutes.

Time of appointment, tenth to fourteenth day of cycle—second month of survey.

Scope of examinations and order:

1. Urethral and cervical smear—Gram stain.
2. Vaginal hanging drop if abnormal vaginal discharge. Examined for trichomonads.
3. Vaginal and cervical pH.\*
4. Low and high cervical postcoital examination for spermatozoa (5 to 15 hours postcoitus).<sup>1, 6, 16</sup>
5. Vaginal smear for glycogen (stained with Lugol's solution).<sup>21</sup>
6. Vaginal smear stained for cornification of vaginal epithelium.<sup>1, 13, 14, 15</sup>
7. Pelvic examination.
8. Schiller's test.<sup>1, 19</sup>
9. Intrauterine postcoital examination.<sup>17, 18</sup>
10. Measurement of height of fundus with uterine sound.
11. Uterine insufflation.<sup>10, 20</sup>

\*BDH Universal Indicator or Gramercy Range Finder—Elmer-Amend.

## SECTION IV. Visit by wife only.

Length of office visit—about 30 to 40 minutes.

Time of visit—third month of survey at fertile phase of cycle.

Order of examinations:

1. Pelvic examination.
2. Vaginal and cervical pH.
3. Vaginal smear stained for cornification.
4. Sperm penetrability.\*
5. 0.5 to 0.7 c.c. of husband's semen injected into the cervix.  
(Semen sample not more than 30 to 60 minutes old.)
6. Intracervical and intrauterine fluid examined for spermatozoa after a lapse of 30 minutes.
7. Recheck of semen analysis from bottle specimen remaining after insemination.

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\*Sample of mucus transferred from cervical canal to microscopic slide. Penetrability to spermatozoa tested by bringing a drop of semen in contact with mucus and observing under the microscope the amount of penetration of mucus.

## SECTION V. Visit by wife only.

Length of office visit—20 to 30 minutes.

Time—Usually twentieth to twenty-sixth day of cycle of third or fourth month of diagnostic survey.

1. Vaginal and cervical pH.
2. Vaginal smear stained for cornification.
3. Low and high cervical postcoital examination for spermatozoa.
4. Pelvic examination.
5. Schiller's test.
6. Intrauterine postcoital examination.
7. Endometrial biopsy.<sup>22</sup>

## SECTION VI. Résumé and correlation of all findings on special analysis sheet given for both husband and wife:

1. Primary diagnosis.
2. Contributing factors.
3. Prognosis.
4. Treatment applied.
5. Treatment recommended.

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the wife is to be on the examination table for other purposes, such as outlined in Section III, IV, and V of the diagnostic survey. While the anamnesis is being taken, the routine blood examination is completed by the technician and the basal metabolic rate calculated. This permits the utilization of information gained from the laboratory work while the patient is still in the office and avoids many repeat visits which might otherwise interfere seriously with the time needed for other cases.

The entire program can be readily carried out in a properly equipped physician's office. No hospitalization is required. Usually a better diagnostic workup is obtained if all of the studies are conducted by a single physician who is particularly interested in the sterility program rather than referring the patient from one specialist to another, many of whom may have little or no interest or experience in the sterility problem as a whole.

Regardless of the group of tests decided upon as constituting a minimal diagnostic sterility agenda, the proper arrangement of examinations will not only facilitate their conduct but will permit a much more comprehensive analysis and a better understanding of the sterility problem than could otherwise be possible.



The omission of such basic tests as those dealing with ovular and spermatie pathology is not uncommon in sterility surveys, and when these or other important basic observations are omitted, a reliable diagnosis is unlikely. Usually, a little advance planning will avoid such omissions without any material increase in time or expense to either patient or physician; and in all but a very small percentage of cases that present some special diagnostic problem, routine examinations for the diagnosis of sterility will be found both practicable and adequate.

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## BREECH PRESENTATION IN THE ELDERLY PRIMIPARA

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**B**REECH presentation has been the subject of numerous contributions in the recent literature, but specific attention has seldom been directed to this type of presentation in the elderly primipara. There have been fifty-five elderly primiparas with primary breech presentations delivered on the indoor service of the Woman's Clinic of the New York Hospital from September 1, 1932, to May 31, 1943. It is the purpose of this paper to review these cases in detail and to give a report of the results found.

In this clinic, a woman thirty-five years of age or over, delivered for the first time of a viable infant, is considered an elderly primipara. During the period of ten years and eight months represented in this study, there were 813 elderly primiparas with viable infants in 29,683 deliveries, an incidence of 2.74 per cent. The incidence of breech presentation in these 813 elderly primiparas is 6.76 per cent. The incidence of breech presentation in the clinic as a whole is 4.72 per cent.

In the group of 55 patients studied 40, or 72.7 per cent, were primigravidas. Nine of the remaining patients had previously had induced abortions, and six had had spontaneous abortions. The number of previous pregnancies were from one to three except in one instance when the patient gave a history of five induced abortions. The 55 patients had a total of 84 pregnancies, 29 or 34.6 per cent of which terminated in an abortion or miscarriage which is a somewhat higher incidence than the usual figure of 20 per cent quoted in the literature. In the entire group only one woman gave a history of relative infertility.

The average age for the 55 patients was 36.9 years; the oldest patient in the study was 42 years. There were 20 private patients, giving an incidence of 36.4 per cent. One patient was colored. There were four sets of twins; the first infant in three sets presented as a breech and in the other set both infants presented as breeches. It is interesting to note that only two, or 3.6 per cent, of the patients delivered on the expected date; 22, or 40 per cent, delivered before, and 31, or 56.3 per cent, after the expected date. The variations from the expected date of delivery were from 60 days before to 30 days after. However, 34 patients, or 61.8 per cent, delivered within a two-week period before or after the expected date. A study of the pelvis in the 55 patients showed an incidence of 12.7 per cent of contracted pelvis as compared to 11.02 per cent in the clinic as a whole.

The following table shows the frequency of antepartum complications of pregnancy in this group as compared with the incidence in the clinic as a whole.

COMPLICATION	INCIDENCE	
	ELDERLY PRIMIPARA WITH BREECH PRESENTATION PER CENT	TOTAL CLINIC PER CENT
Myoma uteri	7.2	1.9
Pyeloureteritis	1.8	1.3
Bleeding in last trimester	1.8	2.3
Toxemia	14.4	11.2
Mild pre-eclampsia	7.2	4.6
Hypertensive disease	3.6	1.2
Unclassified	3.6	1.8
Other types	0.0	3.6

From this table it is evident that the complications of toxemia and myoma uteri are met with more frequently in the elderly primipara group. No patient in this series had syphilis or gave a history of any venereal infection.

In this group of 55 patients, 39, or 70.9 per cent, delivered vaginally. The average duration of labor was 23.8 hours, the shortest labor being 2¾ hours and the longest 86½ hours. Labor was prolonged (30 hours or more) in 21.8 per cent of the cases. In the clinic the incidence of prolonged labor is 9.9 per cent. Sixteen patients, or 29.1 per cent, were delivered by cesarean section. Seven of these patients had some labor prior to the operation, the average duration being 9.4 hours.

A study of the type of the breech presentation shows that frank breech is the most common, 62.5 per cent. Double footling occurred in 10.7 per cent of the cases, single footling and complete breech in 3.4 per cent, respectively, and in 20 per cent of the cases the type was not specified. The most frequent position of the breech was LSA (32.7 per cent); RSA occurred in 27.3 per cent of the cases, and LSP and RSP made up 12.6 per cent of the cases.

Premature rupture of the membranes was noted in 40 per cent of the cases. This means the membranes ruptured before or coincident with the onset of labor. In the clinic a study of 4,250 full-term and premature deliveries of all types showed that the membranes ruptured prematurely in 36.1 per cent of the cases. In Westman's series of 993 breech deliveries, the incidence of premature rupture of the membranes was 32.8 per cent. In spite of the fact that 40 per cent of the patients had premature rupture of the membranes, there were only two patients who developed a puerperal infection. There were no instances of intra-partum infection.

An analysis of the types of analgesia used in the 55 patients shows that nembutal, scopolamine, morphine and rectal ether were used either alone or in combination. However, 30.9 per cent of the patients received no analgesia. The anesthetic administered at the time of delivery was nitrous oxide, oxygen and ether in 83.6 per cent of the cases; the remainder had open drop ether or local, and two patients had no anesthetic.

The following table shows the type of delivery of the 55 patients.

Piper forceps to the aftercoming head were used in 21.4 per cent of the breech extractions, while in the clinic as a whole, the incidence is 14.9 per cent. (External version is not a practice in this clinic.)

TYPE OF DELIVERY	NUMBER OF CASES	INCIDENCE PER CENT
Breech extraction	26	47.3
Decomposition with breech extraction	11	20.0
Spontaneous	1	1.8
Dührssen's incision with breech extraction	1	1.8
Cesarean section	16	29.1
Total	55	100.0

The most outstanding fact in the table is that cesarean section was performed in 16, or 29.1 per cent, of the cases. The incidence of cesarean section in the clinic as a whole is 2.3 per cent, and the incidence of section for the indication of breech presentation is 0.51 per cent. The indications for cesarean section in the 16 cases were as follows:

Acute yellow atrophy of the liver	1
Contracted pelvis	4
Myoma uteri	3
Premature rupture of the membranes	2
Five-year sterility and premature rupture of membranes	1
Previous cerebral accident	1
Breech with extended head	1
Large breech, contracted pelvis	1
Breech presentation	2
Total	16

A post-partum hemorrhage occurred in one of the 55 patients and a manual removal of the placenta was performed. The total morbidity in the series was 18 per cent as contrasted to 9.9 per cent, the total clinic incidence. Premature rupture of the membranes did not appear to be a causative factor in the development of puerperal morbidity, as only two in the 10 febrile cases gave a history of premature rupture of the membranes. Three patients had pyeloureteritis, the febrile puerperium in the others being due to intrauterine infection. There were two maternal deaths, giving an incidence of 3.6 per cent. The mortality rate in the clinic as a whole is 0.198 per cent. Both of these patients died of generalized peritonitis. One was age 38, delivered after 17½ hours of labor by low flap cesarean section, the indication being a contracted pelvis with a large infant. Death occurred on the seventh post-operative day. No autopsy was performed. The other patient was age 36, delivered by classical cesarean section with acute yellow atrophy of the liver as the indication. Death occurred twelve days later. Autopsy showed generalized peritonitis, fatty degeneration of the liver and partial atelectasis.

There were seven infantile deaths in this series, giving an incidence of gross infantile mortality of 12.5 per cent. The incidence in the total clinic for breech presentation is 13.1 per cent. One of the infants, the

second twin of the only instance of both infants being primary breech presentations, weighed 1,570 grams; four weighed between 3,000 and 3,999 grams; and two weighed over 4,000 grams.

The distribution of the weights of the 56 infants (this includes the only second twin presenting by breech) was as follows:

1,500 to 2,499 grams	9
2,500 to 3,999 grams	41
4,000 or over grams	6

The smallest infant in the group weighed 1,570 grams and the largest 4,790 grams. The average weight for the full-term infants was 3,344 grams in comparison with 3,350 grams for the total clinic. It is the opinion of some writers that the elderly primipara tends to have a larger infant.

Two of the infant deaths occurred in patients giving a history of premature rupture of the membranes, and at autopsy the findings suggested death was due to asphyxia. In three of the fetal deaths the mother had received no analgesia during labor. When the histories of the seven infantile deaths are carefully studied, it is noted that all were delivered by breech extraction. Five of the deaths occurred in pregnancies in which labor started two weeks or more past the expected date of confinement, the infants weighing 3,500 grams or over. Labor was desultory and prolonged in these five cases and in two of these a Voorhees bag was inserted to stimulate labor. Three infants were autopsied and the findings were: in the first, multiple small arachnoid hemorrhages; in the second, cephalhematoma and tentorial tears; and in the third, subcutaneous and petechial hemorrhages. Six of the infants were deadborn and macerated at delivery, the seventh one died of prematurity, shortly after birth. The fetal heartbeat was lost in three instances in the first stage of labor, in one case just before delivery, and in three others before the onset of labor. Among the 49 infants discharged well, only one had required resuscitation following delivery, one infant had a subarachnoid hemorrhage, one had a fractured humerus, and one developed hemorrhagic disease.

### Discussion

The elderly primipara with a breech presentation at term is a serious problem that requires careful study of the patient. Accurate pelvic measurements should be obtained and x-ray pelvimetry employed when possible. When the patient is to be delivered vaginally it is not advisable to interfere with the progress of labor by attempts to speed it up. The most unsatisfactory types of labor and poorest results occurred in patients delivering two weeks or more past the expected date of confinement. Elective cesarean section is favored in cases of a large infant, patients overdue two weeks or more with a large infant, and when there is a history of sterility or of repeated spontaneous abortions. Cesarean section should not, as a rule, be the operation of choice when there has



been a desultory type of labor with premature rupture of the membranes or after vaginal manipulation. If a section must be done in such cases, the extraperitoneal type should be performed.

### Conclusions

1. The incidence of breech presentation in elderly primiparas is 6.76 per cent as compared with 4.72 per cent, the incidence of breech presentation in the clinic as a whole.

2. The incidences of toxemia and myoma uteri are increased in the elderly primipara group, being 14.4 per cent and 7.2 per cent, respectively, as compared to 11.2 per cent and 1.9 per cent for the same complications in the total clinic cases.

3. Premature rupture of the membranes occurred in 40 per cent of the elderly primipara group, while in the clinic as a whole it occurred in 36.1 per cent of the cases.

4. There were two maternal deaths in this group of 55 elderly primiparas, giving an incidence of 3.6 per cent for maternal mortality. Both of these patients had a cesarean section, the indications being contracted pelvis with a large infant and acute yellow atrophy of the liver, respectively. The final diagnosis in each patient was generalized peritonitis.

5. The incidence of gross infantile mortality was 12.5 per cent.

6. Cesarean section is indicated in the elderly primipara with breech presentation associated with any one of the following: Large infant, contracted pelvis causing dystocia, myoma uteri, patient two weeks or more past term with a large infant, repeated spontaneous abortions, or a history of sterility.

## GRANULOMA PYOGENICUM OF THE CERVIX

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**G**RANULOMA pyogenicum of the skin is not a rare disease, and occasionally the condition occurs on the lips, tongue and buccal mucosa. Rarely the conjunctiva, bladder or other mucosal surfaces are involved. Reasoning along anatomical and physiological lines, one would expect to find cases occurring in the cervix and vagina, but a careful search of the gynecological literature reveals no reference to this condition. A typical case of granuloma pyogenicum involving the cervix uteri and associated with a marked decidual reaction appears therefore to warrant a brief report.

The disease was first described in 1897 by Poncet and Dor,<sup>1</sup> who designated the condition "botryomycosis humaine." This name was given it because of the similarity of certain mulberry-like masses found in the tumors to those which had been described by Bollinger in the inflammatory scrotal tumors which frequently follow castration in the horse. It was later shown that the mulberry-like masses are not constant in the lesions of this disease and that the most likely causative agent is the ordinary *Staphylococcus aureus*. In 1904 Hartzell<sup>2</sup> proposed the term "*granuloma pyogenicum*," which has been generally adopted in the dermatological literature.

Granuloma pyogenicum is a localized disease of organs covered by squamous epithelium, and not infrequently it follows slight trauma. It is seen most frequently on the hands, fingers, feet, face and buccal mucosa. The lesions are usually single and consist of sessile or pedunculated bright red, inflammatory tumors which vary in diameter from a few millimeters to about 3 cm. They bleed easily and not infrequently emit a foul odor.<sup>3</sup>

The process begins in the subepithelial connective tissue and is characterized by the formation of ordinary granulation tissue which rapidly elevates the epithelium in such a manner as to form a small nodule or tumor on the surface. As the disease progresses, the epithelium is destroyed and granulation tissue grows above the surface, forming a sharply demarcated inflammatory tumor.<sup>4</sup> The lesions are fully formed in the course of a few weeks after their inception.

The skin lesions can be completely cured by wide excision or by the use of carbon dioxide snow. Large tumors are usually treated with roentgen rays, however, since the lesions are very radiosensitive.

Since the tumor of the cervix which we are reporting is identical in every respect with the classical cases of granuloma pyogenicum occurring on the skin, a more detailed description of the microscopic anatomy will be given in the case report.

### Case Report

A 21-year-old white, married female consulted Dr. J. L. Pressly of Statesville, N. C., on August 2, 1943, requesting prenatal care. Her menses had been established at the age of 12 years and occurred every twenty-eight days, with a duration of five days. There had been one previous pregnancy, which was normal in every way and terminated with the delivery of a normal baby in February, 1942.

Her last menstrual period was on Dec. 26, 1942, and her prenatal course was uneventful until March, when she noted slight vaginal bleeding. Examination at that time revealed nothing of consequence, and the source of the blood was not established. The bleeding ceased spontaneously in a few days and did not recur until September 13, when she began to bleed profusely. She consulted her physician, who found a rather brisk flow of bright red blood coming from the vagina.

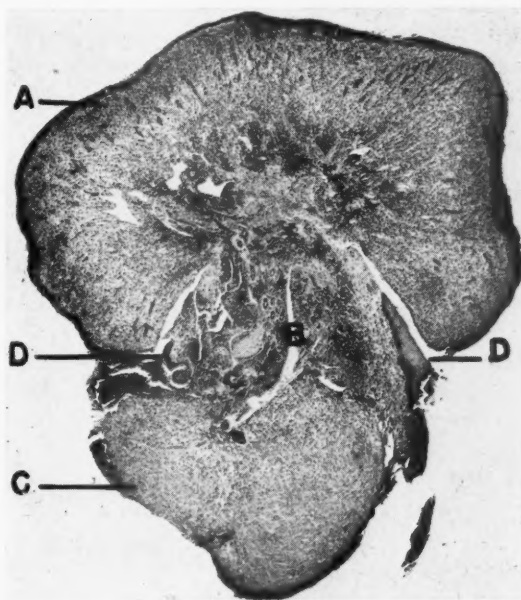


Fig. 1.—The entire lesion. A. The inflammatory tumor. B. Stalk of tumor. C. Decidual tissue. D. Squamous epithelium. ( $\times 13$ .)

Vaginal examination by Dr. T. V. Goode revealed, on the posterior lip of the cervix, a bright red growth which was elevated about 8 mm. above the surface and measured 1 cm. in diameter. It was excised widely, placed in 10 per cent formalin solution, and sent to this laboratory for examination.

The patient was delivered on September 13, and had an uneventful puerperium with no evidence of recurrence of the lesion.

#### *Microscopic Examination:*

Sections through the entire mass (Fig. 1) show a pedunculated tumor (Fig. 1-A) possessing a rather broad stalk (Fig. 1-B) which is con-

tinuous with irregular accumulations of chronically inflamed decidual tissue in the deeper portions of the cervix (Fig. 1-C). On either side of the stalk is a small piece of stratified squamous epithelium (Fig. 1-D), which now occupies a vertical position. One gets the impression of epithelial elevation, followed by destruction and extensive growth above the surface. The inflammatory tumor is composed of prominent and numerous capillaries surrounded by proliferating fibroblasts, neutrophils, plasma cells, monocytes, lymphocytes, eosinophiles, mast cells and fibrin (Figs. 2 and 3). The neutrophile is the predominating cell,

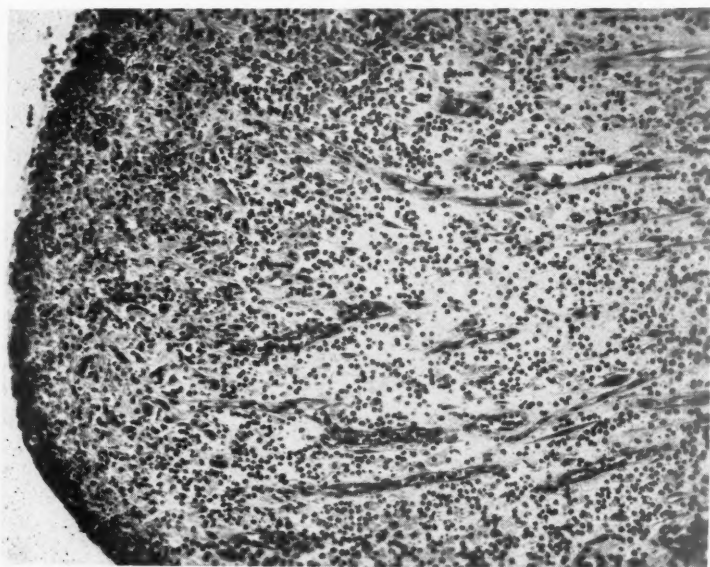


Fig. 2.—Granulation tissue and inflammatory cells. ( $\times 90$ .)

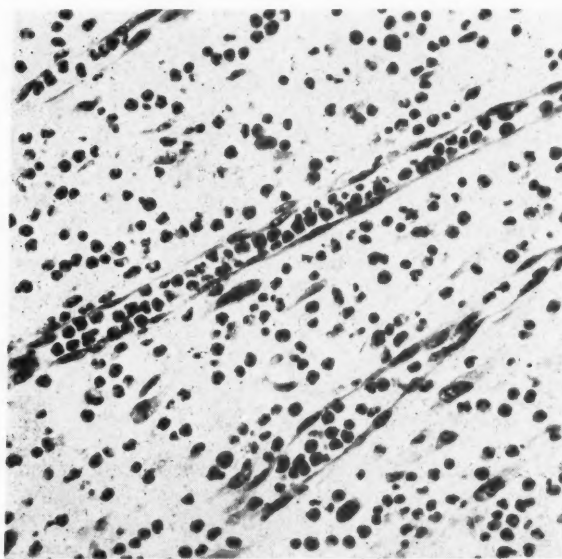


Fig. 3.—Same as Fig. 2. ( $\times 320$ .)

and many young forms are present. On the surface, the tissue has become necrotic and large numbers of neutrophils in all stages of degeneration are present. The capillaries radiate from the stalk to the periphery of the lesion and are filled with inflammatory cells.

The stalk of the tumor is composed of smooth muscle and collagenous connective tissue, along with numerous blood vessels and large accumulations of plasma cells (Fig. 4). Many of the latter are multinucleated, while others can be seen in the various stages of mitosis. The stalk is continuous with irregular sheets of decidua which are infiltrated by a moderate number of plasma cells and neutrophils (Fig. 5).

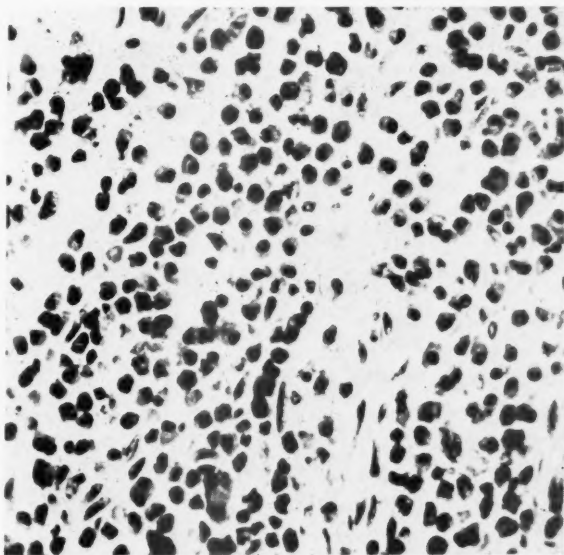


Fig. 4.—Plasma cells. Note that several are multinucleated. ( $\times 320$ .)

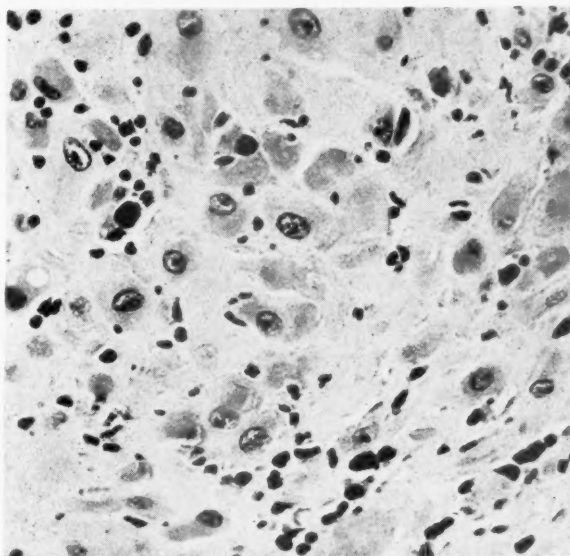


Fig. 5.—Decidual tissue. ( $\times 320$ .)



### Comment

This case is of interest for several reasons. In the first place, it affords an opportunity to study thoroughly a heretofore unrecognized cervical disease. Secondly, it presents an additional example of a rather pronounced decidual reaction in the cervix, which is of extremely rare occurrence. It is of interest still further since it affords an opportunity for speculation as to a possible relationship between the two processes.

We are unable to state with certainty that any relationship exists between granuloma pyogenicum of the cervix and pregnancy. However, the imbibition of the cervical tissues associated with pregnancy may provide a more fertile soil for the staphylococcus, which, in all probability, is the causative agent in this condition. Latzko<sup>5</sup> has pointed out that, although frank decidual reactions in the cervix are extremely rare, they are sometimes observed in connection with markedly inflamed polyps. It is possible that many of the polyps reported in this connection represented in reality examples of granuloma pyogenicum which had been wrongly diagnosed. This erroneous diagnosis may have been due to the examiner's unfamiliarity with the disease, or to the condition of the specimen at the time of its arrival in the laboratory.

The diagnosis of granuloma pyogenicum should be made clinically, for the lesions are very characteristic. If the pathologist is fortunate enough to receive the entire tumor, the microscopic picture is also pathognomonic, but if the specimen is received in a fragmentary or distorted condition, the diagnosis is likely to be missed.

### Conclusions

A case of granuloma pyogenicum occurring in the cervix uteri and associated with a pronounced decidual reaction in that organ is reported. It is probable that the condition is of fairly frequent occurrence, is closely related etiologically to the cervical softening of pregnancy, and is especially likely to appear in the rare cases of gestation which are associated with a frank decidual reaction in the cervix.

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## ECLAMPSIA, CEREBRAL ABSCESS AND HEMORRHAGE\*

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**E**CLAMPSIA, the convulsive toxemia of pregnancy, is characterized by the appearance of edema, hypertension, albuminuria, and convulsions in a pregnant, parturient, or puerperal woman previously free from such symptoms. The etiology of this acute toxemia which has, in the course of time, been ascribed to all manner of causes, both maternal and fetal, is still nebulous. Inasmuch as convulsions and coma are an integral part of the disorder, the differential diagnosis must often include the consideration of intracranial lesions of inflammatory, neoplastic, and vascular origin. The clinical confusion is heightened by the fact that the recurring eclamptogenic convulsions may take on a more localized than a generalized character because of the secondary occurrence of cerebral hemorrhage. The latter is found in approximately 10 per cent of the patients dying from eclampsia.

The following case history illustrates the pitfalls that may be encountered in the differential diagnosis of eclampsia and raises a question concerning the improbable etiologic relationship of eclampsia to a space-taking lesion of the midbrain.

Mrs. S. R. (St. Luke's and Children's Medical Center No. 17271), white, schoolteacher, twenty-seven years of age, thirty-two weeks' pregnant, was admitted to the Hospital during the evening of February 2, 1943, because of a sudden convulsion followed by coma.

The patient had first come under observation three years earlier, in 1940, when she sought contraceptive advice. It is significant that, at that time, the patient had complained of recurring headache of several months' duration, a complaint which persisted and was subsequently attributed to "chronic sinusitis." Except for this long-standing history of headache and an appendectomy at the age of 17, the patient's past medical background held no special interest. A planned pregnancy was initiated during the summer of 1942, the last menstrual period occurring on July 1. The progress of the pregnancy was normal and uneventful, both as reported by the patient and as observed during office examinations on September 15, October 13, November 10, and November 24. The blood pressure, weight increment, urinalysis, and uterine enlargement were perfectly normal at each of these visits; the blood Wassermann reaction was negative. On November 28, at approximately the twenty-second week of gestation, the patient went to Florida for ten weeks, during which period she visited a physician and was pronounced well on three occasions.

The patient returned to Philadelphia during the afternoon of February 2, 1943, stating that she had begun to suffer increasingly severe headache and edema two days earlier. Three hours after her homecoming, she experienced a sudden convulsion, described as "generalized" by lay witnesses, and subsequent coma of one hour's duration.

\*Presented at a meeting of the Philadelphia Obstetrical Society, October 7, 1943.

During the latter period, she was seen by a physician who noted the presence of almost universal, pitting edema and found the blood pressure to be 164/118.

At the time of hospitalization, 8 P.M., February 2, the patient was conscious, exhibited evident edema of the face and limbs, had a blood pressure of 148/112, and complained of headache. A specimen of urine, obtained by catheterization, showed a dense cloud (four plus) of albumin. The uterus extended to three fingerbreadths above the umbilicus, the presentation was a vertex, and fetal heart tones were clearly audible. The treatment administered on admission included 10 c.c. of a 20 per cent solution of magnesium sulfate intramuscularly, 100 c.c. of a 50 per cent solution of glucose intravenously, one-quarter grain of morphine sulfate hypodermically, a soapsuds enema, gastric lavage until clear, and 2 ounces of a saturated solution of magnesium sulfate orally. Despite an evident oliguria, the patient improved during the night—the edema was notably less, the blood pressure fell to 136/106, and the headache was alleviated. Labor, induced by rupture of the membranes, began at 6 P.M., February 3, was normally progressive, and was terminated 15 hours later—9 A.M., February 4—with the spontaneous birth of a living, male child in very poor condition. The baby, 15 inches in length and 2 pounds, 12 ounces in weight, lived but one hour.

The patient's immediate post-partum course was afebrile and, aside from the frequent complaint of headache of the left frontal area, was uneventful. The daily blood pressure readings ranged between 100/70 and 140/90, the albuminuria disappeared, and a complete laboratory survey of the blood chemistry and blood count revealed no abnormalities. Thorough examination of the nasal sinuses failed to reveal signs of infection as a cause of the persisting headache. The patient was out of bed on the ninth post-partum day, February 12. That evening she appeared to be abnormally drowsy. The following day, February 13, the patient's headache was more severe, weakness of the right arm was noted, and drowsiness was evident. A day later, February 14, a neurological examination disclosed slight nuchal stiffness, bilateral Kernig's sign, and a definite hemiparesis of the right side. The clinical impression, then, was that the patient had either a moderate subarachnoid hemorrhage or cerebrovascular spasm as a result of the eclampsia. Treatment included 20 mg. of thiamin chloride and 100 mg. of niacinamide intravenously daily, as well as one-quarter grain of papaverine orally three times daily. A lumbar puncture, performed on February 15, yielded 12 c.c. of clear, distinctly xanthochromic, cerebrospinal fluid which was shown to contain 600 erythrocytes and 800 leucocytes (chiefly polymorphonuclears) per cu. mm. On February 16, the patient was deeply stuporous. Neurological examination revealed the signs of a left cerebral lesion, presumed to be either hemorrhage or an acute encephalitis as a result of an infected embolus. There was little to support the latter diagnosis, inasmuch as the patient was afebrile, had no leucocytosis, and presented perfectly normal genital organs.

The patient never roused again. She was supported by means of gavage feedings, and was given 100 c.c. of 50 per cent solution of sucrose and 10 mg. of vitamin K intravenously twice daily. She expired on February 20, the sixteenth post-partum day. A retrospect study of the clinical record uncovered the significant fact that, during the last week the patient had a distinct bradycardia, the axillary temperature being fairly steady at 99.5° F., and the pulse rate being 60, with occasional drops to 50, per minute.

*Post-mortem Examination.*—The only organ which showed relevant changes, at autopsy, was the brain. It is significant that the pelvic organs were entirely free from signs of infection and that the liver, on histologic study, was devoid of periportal hemorrhage and necrosis, the lesions so characteristic of eclampsia.

The brain was large. The frontal section showed a fresh abscess involving the left frontotemporal area, beginning at the level of the anterior pole of the lateral ventricle and extending from the posterior part of the frontal lobe throughout the entire extent of the temporal lobe. The abscess cavity measured 3 by 9 by 2 cm. It had a poorly defined wall and practically no capsule, giving the impression that it was acute. The abscess lay deep under the cover of the insula, and involved the region of the left lenticular nucleus adjacent to the internal capsule. It had destroyed the left thalamus and the posterior limb of the internal capsule. The anterior portion of the abscess contained pus and blood. On its medial aspect, adjacent to it, was a recent hemorrhage involving the internal capsule and basal ganglion.

A culture of the pus in the abscess cavity yielded a growth of pure pneumococcus.

#### Comment

The history of a twenty-seven-year-old, white female is related, delineating the occurrence of eclampsia at the thirty-second week of gestation, followed by the premature birth of a child who lived but one hour. The post-partum course of the patient was noteworthy because of the appearance of coma, right hemiparesis, and death. The autopsy disclosed the presence of a large cerebral abscess and an adjacent area of hemorrhage.

2116 SPRUCE STREET  
111 N. 49TH STREET

## ERYTHROBLASTOSIS FETALIS IN IDENTICAL TWINS

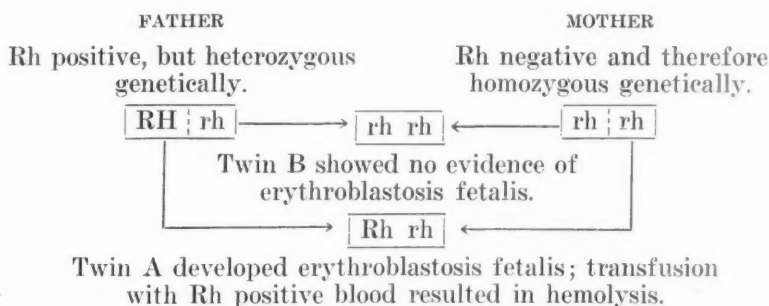
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(From the Department of Obstetrics of the New York Polyclinic Hospital)

**A**LTHOUGH we are quite certain that the cause of erythroblastosis fetalis has its inception in genetic differences between the mother and father, there is by no means complete agreement in its mode of transmission. According to Levine, no great number of red cells is necessary to sensitize the mother provided the proper Rh factor conditions are present, and that such a number can be accounted for on the basis of diapedesis alone. Placental defects characterized by infarcted areas and the persistence of Langhans' cells have been described. The origin of these defects is unknown; capillary fragility from avitaminosis C has been postulated though the case to be described would throw doubt on this assumption.

Not every union of an Rh positive father and an Rh negative mother results in erythroblastosis fetalis, nor are the clinical pictures in the infant identical in every case, so that the placenta does figure in its pathogenesis. The differing prognoses in icteric, anemic, hemorrhagic, and hydropic forms indicate varying degrees of sensitivity and levels in the titer of antibody in the mother.

Kariher reported in the July 31, 1943, issue of the *Journal of the American Medical Association* a case of erythroblastosis fetalis in one of double ovum twins, the other being normal. The affected twin was transfused with the father's blood and died. Since the Rh positive factor is a Mendelian dominant, the following scheme probably represents the mechanics in this case:



The present case resulted in a forty-year-old gravida vii, para vii, who had had four successive living infants in 1924, 1927, 1929 and 1932. In 1934, she gave birth to twins, one of whom was stillborn; the other lived four hours, dying of hemorrhage. In 1936, she gave birth to a sixteen-pound stillborn child, and though no data are available other than that hemorrhage was present, we may assume this to have been a case of fetal hydrops. Erythroblastosis fetalis was suspected in the present gestation, and a diagnosis of twins was made before delivery. The father's blood proved to be Rh positive; the mother's Rh negative in high titer. Labor resulted in the normal spontaneous delivery of living twin girls. There

\*At present in Service with the Armed Forces.



were a single placenta, single chorion and two amnions so that these were identical twins. Microscopic examination failed to reveal anything abnormal.

Twin A weighed 5 pounds, 8 ounces, and was jaundiced at birth, petechial hemorrhages appearing all over its body within twenty-four hours. Its spleen and liver were greatly enlarged and hard. Blood count on the first day:

R.B.C. 1,560,000, Hemoglobin 40%, W.B.C. 164,000, Pmn. 49%, Lymphocytes 47%, Myelocytes 2%, Metamyelocyte 2%, Polychromatophilia: Marked, Achromia: Marked, Anisocytosis: Moderate, Poikilocytosis: Moderate, 321 Normoblasts/100 W.B.C., 27 Megaloblasts/100 W.B.C.

One hundred c.c. of blood from an Rh negative male donor were given into the anterior fontanelle. Intramedullary transfusion was unsuccessful probably due to hyperplasia of the marrow. A count on the second day showed:

R.B.C. 3,160,000, Hemoglobin 68%, W.B.C. 26,600, Pmn. 68%, Lymphocytes 24%, Eosinophiles 1%, Myelocytes 2%, Metamyelocyte 2%, 55 Normoblasts/100 W.B.C.

A second transfusion of eighty c.c. was given into a scalp vein. The count following this was:

R.B.C. 4,190,000, Hemoglobin 81%, W.B.C. 4,400, Pmn. 67%, Lymphocytes 25%, Myelocytes 6%, Metamyelocyte 2%, 49 Normoblasts/100 W.B.C.

Subsequent counts were within normal limits. One week after delivery the icterus index was 85. Since the child was not doing well despite the normal counts, another transfusion of ninety c.c. was given followed in three days by an additional one hundred c.c. Vitamin K, copperin B and liver extract were given empirically. On the fifty-first hospital day, twin A was discharged with a deep mahogany-colored skin, slightly enlarged liver and spleen and a weight of 6 pounds 4 ounces.

Twin B weighed 5 pounds, 14 ounces at birth, and was also jaundiced though to a much lesser degree. Spleen and liver were not remarkable. Blood count on the first day:

R.B.C. 4,550,000, Hemoglobin 90%, W.B.C. 21,600, Pmn. 72%, Lymphocytes 24%, Myelocytes 4%, Poikilocytosis: Moderate, 34 Normoblasts/100 W.B.C.

One hundred c.c. of Rh negative blood from a male donor were transfused into the anterior fontanelle. Blood count on the third day:

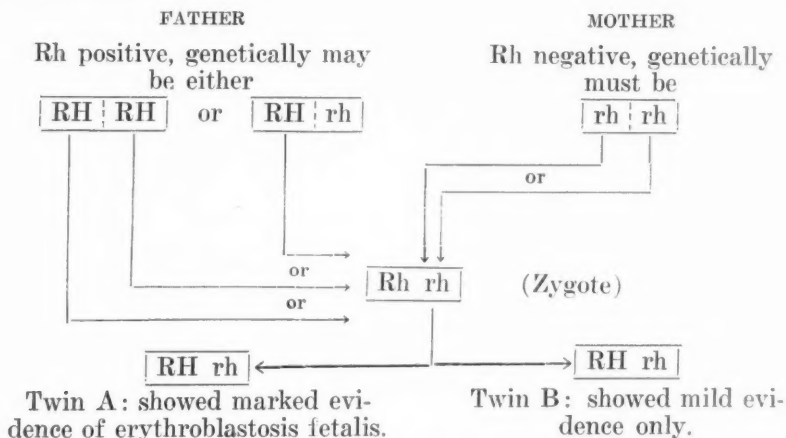
R.B.C. 4,000,000, Hemoglobin 79%, W.B.C. Q.N.S., Pmn. 36%, Lymphocytes 50%, Myelocytes 8%, Metamyelocytes 6%, 40 Normoblasts/100 W.B.C.

It was also given vitamin K, copperin B and liver extract but no further transfusions. Subsequent counts were normal. On the fifteenth hospital day, it was discharged weighing, 5 pounds 12 ounces. Latest report is that they are both doing well and thriving.

### Comment

It is not certain whether the father is genetically hetero- or homozygous since the first four normal offspring might have occurred in the absence of a placental defect, lack of sensitization of the mother, or low titer of antibody. The last pregnancy resulted in single ovum twins, so that they had identical genetic inheritance, were both Rh positive and

therefore subject to the same titer of antibody from the mother; yet one developed a severe hemorrhagic form of the disease whereas the other reacted only mildly and might have escaped notice were it not for the history of the case and the condition of its twin. One can only conclude that the portion of the placenta serving twin A had a greater functional defect than that serving twin B, resulting in more massive exposure to antibodies from the mother. The following is probably the sequence in this case:



## A CASE OF INCARCERATED UTERUS SUCCESSFULLY TREATED IN 1808

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**I**NCARCERATION of the pregnant uterus is not a common complication of pregnancy. When present it can usually be successfully treated by modern methods even if laparotomy has to be resorted to. However, previous to our time, before the development of aseptic techniques, the successful treatment occasionally offered many difficulties. In reviewing the present case we are reminded of another instance in the annals of medical history the significance of which was truly great. This was the celebrated case of Mrs. Merrill of Montgomery, Alabama, who was successfully treated by Dr. J. Marion Sims. It will be recalled that the invention of the Sims speculum and the development of a cure for vesicovaginal fistula were the direct result of Sims' experience, and when we consider his eminent and spectacular career from that time forward, we are inclined to hazard a view that Mrs. Merrill ought also to have her niche, even if a small one, beside her famous compatriot Jane Crawford.

The case here reprinted is interesting from two points of view: first, because of its early record and, second, because of the method used in its successful treatment. It was apparently the author's wish to remain anonymous, for he chose to sign his contribution, "A Member of the Society," and a cursory search has not revealed his identity. He remains, therefore, as he wished it, unknown. The story begins in the year 1809, when, at a Convention of the Fellows of the Medical Society of the State of Connecticut a committee was appointed to select pieces for publication from such communications as were then in the possession of the Secretary and publish them before the meeting of the next convention. The result was the publication in 1810 of a collection of fourteen papers, all of which were signed except the one referred to here. Among the authors we find names notable in American medicine. Lemuel Hopkins, a pioneer in the treatment of tuberculosis and a "Connecticut Wit," Eli Ives, a founder and professor of the Yale Medical School and one time President of the American Medical Association, and William Tully, "unrivalled in his knowledge of the materia medica" and important as a medical educator. The final item in the Table of Contents is a Case of Retroverted Uterus and appears as follows in the text:

*"The following case of retroverted Uterus may be important, on account of the simple means used to restore the Uterus.*

"September 23, 1808, Mrs. A----- of New Haven, a woman of forty years of age, the mother of eight children, in jumping from a horse, felt something give way in the pelvis; at this time she supposed herself to be about three months advanced in pregnancy. The shock was followed by great weakness; sensation of bearing down, costiveness, dysuria, nausea, and vomiting, and all the train of hysteric symptoms, arising from the stomach, sympathizing with an irritating and inflamed uterus. These symptoms were supposed by the patient to arise from her pregnancy, and of course were endured with patience, until they increased to a very alarming degree. A period of fifteen days elapsed, during which she took a

little castor, valerian, etc. At this time she was examined. Entering the vagina, the finger met a tumor twice the size of a hen's egg, between the vagina and rectum, pressing itself forward into the vagina, and occupying two-thirds of the os externum. A finger of the other hand was passed into the rectum, by which it appeared that this tumor was a sack of the rectum filled with indurated feces, which sack had been formed by the pressure of the superincumbent uterus; passing the finger into the rectum, a little farther up, the rectum was entirely obstructed by the fundus of the uterus, beyond which the finger could not pass, and on which it could make no impression. The uterus at the same time was felt by the finger in the vagina, wedged firmly between the sacrum and pubis and the os tincae, in the superior and anterior parts of the vagina. At this time the stomach could retain nothing—strong spasms agitated the system frequently; bowels were full and tense, particularly above the pubis; frequent inclination to pass urine and stool, with much pain and distension in the pubis. The urine had been entirely obstructed; but for two or three days past the patient thought she had passed the usual quantity of urine; however, the catheter was introduced, and eight pounds and three ounces of urine drawn off. The rectum was also emptied. The patient was laid upon her back, her hips raised; in this position, with two fingers in the vagina, and two in the rectum, exertions were made to restore the uterus, until her physicians were satisfied that it could not be restored in this manner. The patient was placed on her knees and elbows, and repeated trials made to restore the uterus, but with no better success. The uterus was finally restored by an instrument resembling a probang, made of a cylinder, the size of the finger, and eight or ten inches in length, on the end of which a head was formed, by winding flax and covering it with soft leather, as large as could be passed into the rectum. With this instrument, oiled and introduced into the rectum, the patient on her knees, the thorax lower than the pelvis, two fingers in the vagina, and much force applied by the instrument and fingers, the uterus was raised above the brim of the pelvis. The patient was enjoined rest and a recumbent posture; and after the usual period of gestation, was delivered of a healthy child.

“New Haven, July 10, 1810.”

“A Member of the Society.

In the above case it will be seen that the author first used without effect the technique later successfully applied by Sims. It remained, therefore, for him to exercise an ingenuity which he probably came by through his Yankee forbears.

## UTERUS BICORNIS UNICOLLIS WITH ASSOCIATED STERILITY CORRECTED BY SURGERY\*

J. R. EISAMAN, M.D., PITTSBURGH, PA.

**B**ECAUSE of infertility during six years of married life, Mrs. B. (No. 60097) sought medical advice in December, 1940. She was then 32 years of age and had never been pregnant.

Her general physical examination, health and habits were normal. Laboratory and endocrine studies were also normal. Her husband was well, sexually potent and fertile as judged by Hühner test and seminal analysis. However, what was thought to be a small fibroid was detected to the right of the cervicofundal junction of the uterus. This tumor was not larger than  $1\frac{1}{2}$  inches in diameter.

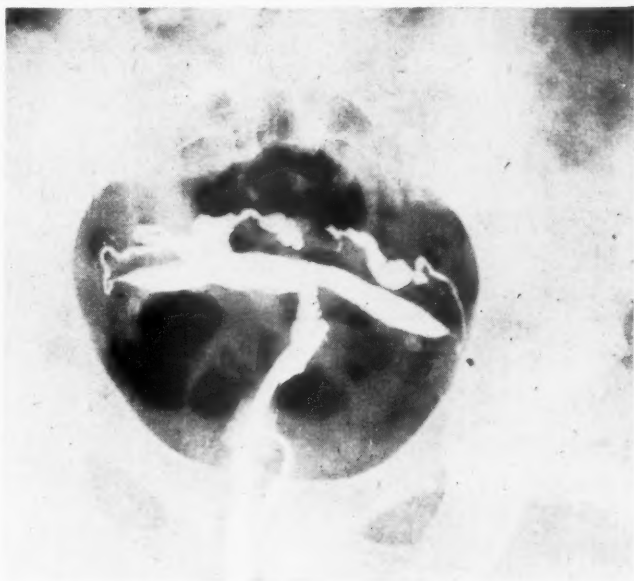


Fig. 1.—Position of uterine cornua before operation.

In April, 1941, after some months of effort on the part of Mrs. B., her husband, and her physician, it was decided to remove the one possible cause of her sterility, the *small fibroid*. She was admitted to a hospital for operation. Fortunately, the uterus was injected with iodized oil before laparotomy and a bicornuate uterus was apparent. Because of the extreme lateral flexion of the uterine horns, a stem pessary was inserted into the right side of the uterus in June, 1941, and retained for 6 months.

About March, 1942, her family physician found tenderness about her right lower abdominal quadrant and suggested an appendectomy. The operation was duly performed and an incidental uterine plastic opera-

\*Read before the Pittsburgh Obstetrical and Gynecological Society, Dec. 6, 1943.



tion also was done. This consisted of stripping the peritoneum from the superior surfaces of the uterine horns, approximating the organs and anchoring them with silk sutures. By so doing, the component parts of the uterus were brought into an upright and more normal position.

After a rather short interval at home she complained of amenorrhea and a positive Friedman test was obtained. As prophylactic measures, wheat germ oil, corpus luteum (orally and intramuscularly) were administered and continued until the fetus was viable.

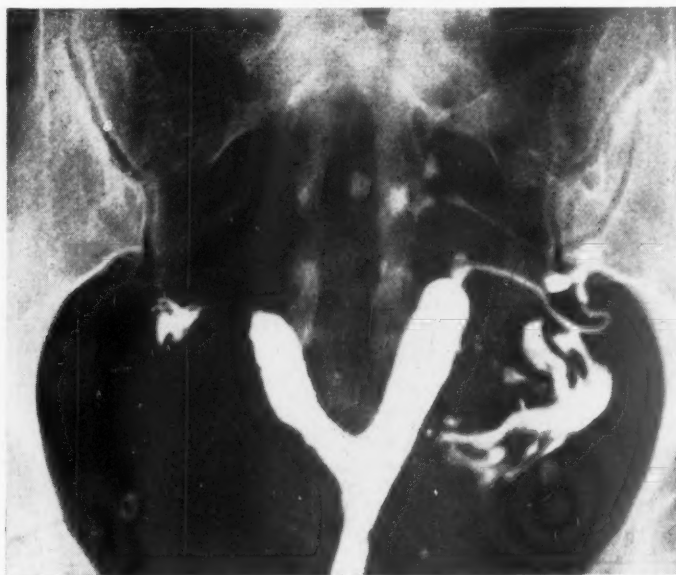


Fig. 2.—Relative position of cornua ten weeks after delivery of infant from larger right horn.

In August, 1943, she was admitted to the hospital, one week before the expected date of confinement, to be prepared for cesarean section. The day before operation was planned, an inertial labor began and a low classical cesarean operation was done, after a labor of four hours. At operation the fetus was found within the right cornu of the uterus, the left remaining quite distinct but closely attached to the other. A 7-pound 3-ounce living male infant was delivered. The placenta did not separate spontaneously after the use of intravenous pitocin. When removed manually, it was found to be attached to the mesial surface of the right cornu. The myometrium of this horn was noted to be flabby and so thin that the gloved hand was apparent through the wall.

Although this case is interesting because of the apparent effectual relief offered to this patient by partial correction of the uterine anomaly, it is not unusual as this condition is reported to be found once in every 1,500 obstetrical and again in every 2,000 gynecological cases.

# Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

## ADVANCES IN ENDOCRINE THERAPY\*

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ENDOCRINE therapy is one of the newest branches of medicine. Its scope is enlarging and changing constantly. Almost daily new claims are made and previously current procedures discarded. In what follows, I shall present to you what I consider sound practice as of today.

An attempt at endocrine therapy was made in 1889, when the famous, peripatetic physiologist, Brown-Séquard, described the rejuvenescent effects of a crude testicular extract which he had prepared and used upon himself. Many years passed before effective androgenic therapy was developed, but in the interim his example was followed by numerous imitators.

Effective endocrine therapy may be said to have originated in 1891, a mere fifty-two years ago, when Murray used a glycerin extract of fresh sheep thyroid glands upon a woman afflicted with severe myxedema. Shortly thereafter he changed to desiccated thyroid substance, a remedy which we still use. As a result of this striking success, the lay public since has been fed, *ad nauseam*, with desiccates of all the endocrine glands, as well as with splenic, mammary, placental and prostatic substances.

TABLE I CHRONOLOGICAL REVIEW

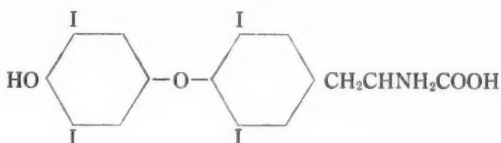
1891	<i>Thyroid Extract</i>	Murray
	1914—Thyroxin	Kendall
1895	<i>Pituitrin</i>	Sharpey-Schafer
	1928—Pitocin, Oxytocin	Kamm
1901	<i>Epinephrine</i>	Aldrich, Takamine
1922	<i>Insulin</i>	Banting and Best
	1935—Protamine Insulin	Hagedorn
1925	<i>Parathormone</i>	Collip
	A T 10	
1928	<i>Chorionic gonadotropins</i>	Aschheim and Zondek
1929	<i>Crystalline estrone</i>	Doisy
	1938—Stilbestrol	Dodds
1932	<i>Androsterone</i>	Butenandt
1934	<i>Progesterone</i>	Slotta, etc.
1936	<i>Desoxycorticosterone</i>	Reichstein

The endocrine extracts, as well as the pure crystalline products employed in therapy, may produce clear-cut effects. Nevertheless, this need not signify that they represent the hormones exactly as they exist and act within the living organism where they most probably are linked to large protein molecules. This is well illustrated by the thyroid hor-

\*Address at a meeting of the Mount Sinai Hospital, November 24, 1943.

mone to which I shall refer presently. Another example is at hand in epinephrine, a comparatively simple chemical entity which exerts a multitude of pharmacologic actions. I always have considered it a *partial* hormone, a fragment let us say, forcibly torn from a larger and more complex body which in nature exerts functions different and more subtle than those of the drug we use in medicine.

*Thyroid.*—I have already mentioned the use by Murray of desiccated thyroid substance. This same drug still is widely employed, mainly in the treatment of thyroid deficiency of which cretinism and myxedema are the best examples. It also is applied in the treatment of obesity as an adjuvant to a reducing diet. It has proved effective in the relief of retardations of growth and development in childhood and adolescence, as well as in all conditions accompanied by reduction of the basal metabolism, no matter what their origin, because of its calorogenic action which causes the cells to metabolize at a higher rate and accelerates the combustion of all the foodstuffs. It should not be employed, or only with great caution, in states of malnutrition.



Thyroxin

Fig. 1.

In 1914, Kendall isolated a pure chemical entity known as thyroxin (a tyrosene compound). This substance exhibits the same therapeutic properties as the gland desiccate. A closely related compound, also obtained from the gland, is diiodotyrosin, which, pharmacologically, is almost inactive. The modern concept may be formulated somewhat as follows. The thyroid produces thyroxin and diiodotyrosin in combination with a large protein group (globulin) to form a molecule of 675,000 molecular weight. Our crude concentration and extraction methods tear off fragments, of which one, thyroxin, retains pharmacologic activity. I have found no advantages over thyroid extract, attributable to the use of thyroxin. More recently an active substance of increased potency has been prepared by iodination of protein of nonthyroid origin (Reinecke and Turner).

In prescribing thyroid extract, it is well to remember that children and adolescents show marked tolerance to the drug and may require disproportionately high dosage. On the other hand, after forty, particularly in the presence of cardiovascular and renal diseases, undue sensitivity and atypical response may be anticipated and should be guarded against. Other less common uses of thyroid extract will be mentioned later.

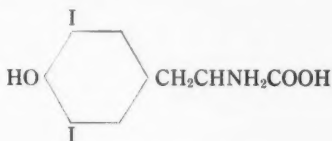
In this connection the palliative use of iodine in hyperthyroidism and in the mass treatment for the prevention of endemic goiter (Marine, 1921) deserve at least mention. The recently advocated treatment of hyperthyroidism, by means of thio-uracil, does not fall within the frame of my discussion.

*Posterior Pituitary.*—In 1895 Sharpey-Schafer discovered "pituitrin." Not until 1928 was the extract sufficiently purified to permit

Kamm to separate it into two fractions, oxytocin and vasopressin (pitressin). Oxytocin acts upon the uterine musculature; vasopressin contracts the peripheral blood vessels, stimulates intestinal peristalsis and also contains the antidiuretic factor.

For the past forty years, pituitrin and, for the last fifteen years, its two factors (oxytocin and pitressin) have proved useful pharmaceutical agents. Obstetricians initiate labor at term by injecting repeated, graduated doses either subcutaneously or intravenously; control postpartum bleeding at cesarean section, after labor or abortion. Surgeons employ it to stimulate the sluggish or parietic intestine postoperatively. It is a powerful drug which must be used with caution. Dystocia, employed in its broadest meaning, definitely contraindicates the use of pitressin, because uterine or intestinal rupture may result if an obstruction exists.

Posterior lobe extracts have a more strictly endocrine application in controlling the excessive diuresis of diabetes insipidus. Here the extract acts in a substitutional role, replacing the deficient antidiuretic factor. Not only subcutaneous but also sublingual and intranasal application proves effective. Pitressin tannate, by subcutaneous injection, is said to have a more prolonged action.



Diiodotyrosine

Thyroglobulin Molecular Wt. 675000

Fig. 2.

Intermedin, a product of the intermediate pituitary lobe which is well marked in some species (first described by Zondek in 1932), has shown in my hands, no superiority to the other posterior extracts in the treatment of diabetes insipidus.

*Adrenal Medulla: Epinephrine.*—The first chemical identification of any hormone was achieved almost simultaneously and independently by Aldrich and Takamine in 1901. Epinephrine or adrenalin proved a popular drug in temporarily elevating the blood pressure in collapse. It soon became apparent that continued intravenous administration proves dangerous because of the sudden and permanent depression of blood pressure which supervenes. Epinephrine shows a paradoxical reaction on the bronchial musculature, relaxing spasm and therefore proving useful in the relief of asthma. In hay fever and obstructive coryza, epinephrine sprays shrink the engorged turbinates. Because of its local vasoconstricting action, today the main use is to prolong local anesthesia by confining the anesthetic to circumscribed areas.

In passing I might say that this is neither the place nor have I the courage to enter into the still hotly debated field raging about the physiologic properties of epinephrine which include its widely varied effect upon the various unstriped muscle groups, its role in maintaining tonus, its manifold influences upon the autonomic nerves and centers, as well as upon metabolism. Except for its local ischemic action, epinephrine has been superseded largely by other new synthetic drugs (Fig. 3).

**Pancreas.**—Long anticipated, feverishly sought after, insulin finally was obtained in 1922, by the combined efforts of a surgeon and physiologist, Banting and Best. With its discovery, the huge and widespread group of diabetics found relief and safety. In 1935, Hagedorn introduced protamine insulin, a more prolonged-acting insulin. The control of diabetes has become a special branch of endocrinology upon which I shall not venture.

My experience with insulin in conditions of malnutrition and in the treatment of dysmenorrhea, for which it was recommended, has been disappointing. Insulin likewise is employed in the production of hypoglycemic shock in the treatment of schizophrenia.

**Parathyroid.**—Three years after the discovery of insulin in 1925 Collip, who had contributed greatly to making insulin clinically available by eliminating its protein contaminant, announced a parathyroid extract with which he controlled the toxic phenomena occurring after parathyroid deprivation. The extract is crude and rapidly produces an increasing resistance or immunity which the discoverer ascribes to an "antihormone" action. Parathormone is of value during the critical

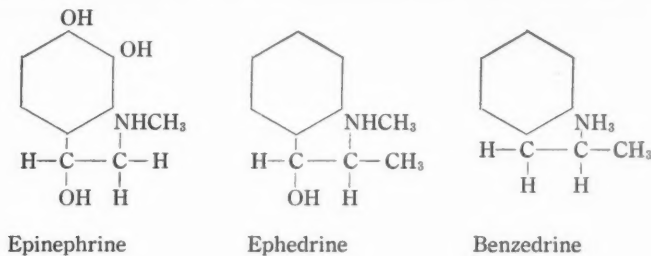


Fig. 3.

postoperative days following a partial removal of parathyroid tissue, either accidental or designed. In the acute stage it controls tetany and averts death. In chronic parathyroid deficiency, the rapidly increasing resistance to the drug necessitates the simultaneous exhibition of dihydrotachysterol, a reduction product obtained from irradiated ergosterol, known also as A T 10. However, A T 10 alone was unable to keep the one patient whom I was privileged to watch for many years, in complete calcium equilibrium even when huge doses of vitamin D were given simultaneously. The combination of parathormone in small doses with A T 10 kept her in perfect health.

According to Silbert, some relief, and in early cases, partial arrest, may be obtained in scleroderma by the continuous, cautious exhibition of A T 10. As the drug increases the blood level of calcium, excessive elevation must be watched for and guarded against.

**Anterior Pituitary and Related Substances.**—The gonadotrops include extracts of the prepituitary gland or adenohypophysis, concentrates of the blood serum of pregnant mares, and the chorionic gonadotropins, derived from pregnancy urine. None of these have been purified; their chemical structure is unknown.

Through the pioneer work of Philip E. Smith and simultaneously that of Bernard Zondek in 1927, the stimulating and regulating action of the anterior pituitary gland upon the gonads—both ovaries and testes—was discovered. Since then many other properties of the hypophysis have been demonstrated but these do not as yet warrant general clinical



application. I refer to the lactogenic, thyrotropic, adrenotropic, growth stimulating, ketogenic, and other factors which may be clearly demonstrated in the laboratory.

Up to the present, none of the products obtained from the anterior lobe itself deserve clinical consideration. I state this categorically despite the glowing reports found in the literature; I base my opinion upon extensive and controlled trial and observation.

The serum of pregnant mares obtained a transient popularity in the treatment of sterility. It was injected intravenously in order to produce ovulation. Today a much more cautious attitude is observed. Personally, in a well-controlled clinical experiment, I have never been able to demonstrate that it produced ovulation in women.

The chorionic gonadotropins obtained from the urine of pregnancy are useful in initiating the descent of cryptorchid testes, particularly in the age group of six to twelve years. Approximately twenty-five per cent of the patients respond by permanent descent of the testes into the scrotum. I give 100 units intramuscularly three times weekly for from seven to eight weeks. If there is no result, it is well to wait six months in order to permit the refractory phase to diminish and then give 1,200 units subcutaneously at one injection. This large dose, even if unsuccessful, will cause localized pain at the site of the hidden gonad and thus guide the surgeon in planning his operation. Today it is almost obligatory to precede operation for undescended testicle by adequate gonadotropic therapy.

The control and even cure of menorrhagia and metrorrhagia by means of chorionic gonadotropins were accepted almost without dissent a few years ago. Today all careful observers agree that this hope was illusory. This affords a striking example of the *post hoc* and *propter hoc* attitude which has so frequently misled in endocrinology, and which is due to loose thinking, lack of critique, and inability or unwillingness to differentiate between success due to coincidence or to therapy. The same disillusion applies to many other uses recommended for gonadotropins.

*The Steroid Hormones.*—The chemical structure of the steroid hormones was rapidly clarified by the work of many biological chemists. The foundation for this stupendous advance was based upon the observation of S. Loewe and Lange in 1926, that the urine contained estrogenic substances. From this readily obtainable and water-soluble source, free from many contaminants of similar solubility to that of the steroid hormones contained in the tissues, Doisy, in 1930, crystallized a pure estrogen. In rapid succession investigators determined the structure of the estrogens, androgens, progestins and adrenocortical hormones. They all were found to belong to the general group of cyclopentenophenanthrenes, a group closely related to the universally distributed cholesterol.

How useful to the clinician have these new, potent hormones proved? It is well to bear in mind that all the steroid hormones, not only react upon their end organs or, the term of today, their "target" glands, but also affect the anterior pituitary by diminishing its output of stimulating or excitatory factors. Therefore exhibition of a sufficient quantity of estrogen, for example, to a menstruating woman, will disturb the rhythm of her cycle because it depresses the production of the stimulating gonadotropic hormone of the prepituitary though it directly stimulates the uterine tubular tract. Given to an amenorrheic female, it similarly depresses the anterior pituitary action, and therefore must depress follicle growth simultaneously, thus defeating the very purpose for which the

clinician prescribes the drug. Analogous depression of hypophyseal action results when progestin, androgens or adrenocortical hormones are given, the depression being very specific upon the various hypophyseal factors.

*Estrogens.*—A number of natural estrogens are available. Of these, estradiol and its benzoic ester are the most powerful. Estrone is next in strength. Estriol is the weakest. In addition, we now have a cheap synthetic estrogen, diethylstilbestrol (commonly called stilbestrol) as well as hexestrol (Fig. 5). The action of both natural and synthetic estrogens is identical.

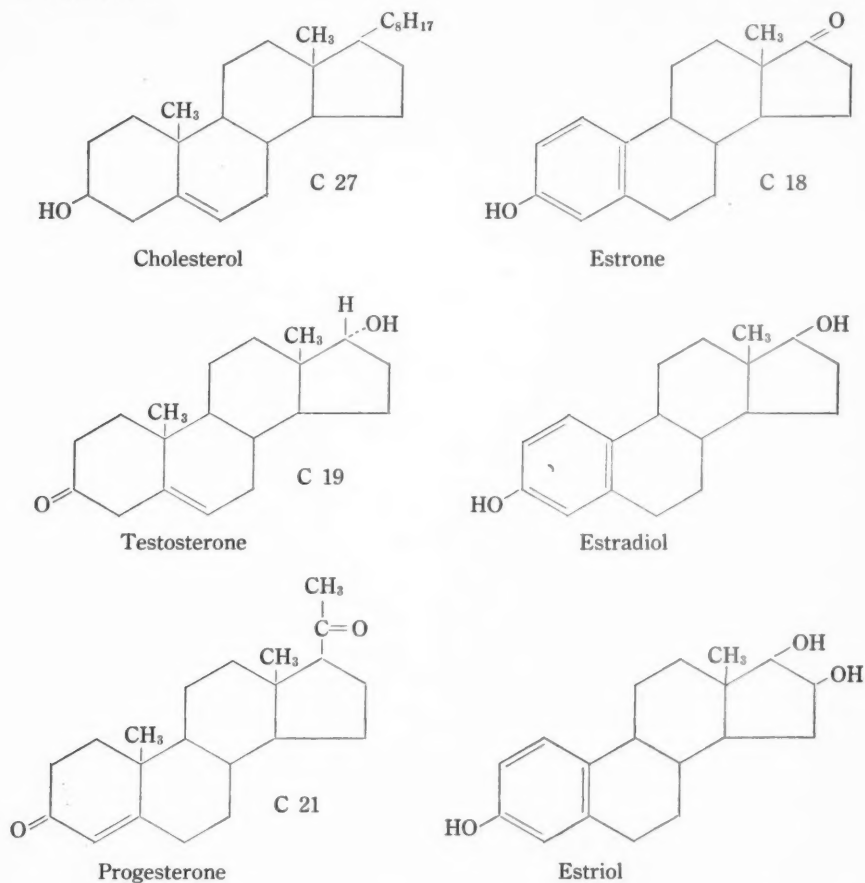


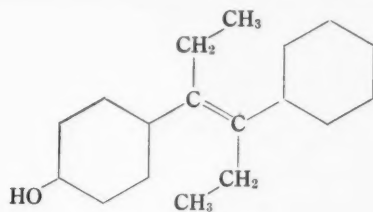
Fig. 4.—Structural formulas of cholesterol and steroid hormones. All have in common the cyclopentenophenanthrene nucleus.

After many years of wild and often senseless clinical application, the indications for the employment of estrogens have contracted to the following, first and foremost, the relief of the neurovascular, arthritic and nervous symptoms of the menopause. Estrogens are contraindicated in the preclimacterium, even if menstruation is no longer regular and flushes are complained of. If given at this time, excessive and more irregular bleeding may be anticipated, and indefinite prolongation of the climacteric condition may be induced, extending over many years. I have seen women of seventy, who still required or believed that they re-

quired estrogenic therapy. The giving of estrogens during the *pre-climacterium* is one of the commonest errors of which both specialists and general practitioners are guilty. I see many patients who, as a result of this mistaken treatment, exhibit bizarre mixtures of menorrhagia, metrorrhagia, leucorrhea, painful and lumpy breasts, etc.

Estrogens, preferably in the form of vaginal suppositories, exhibited over ten to fourteen days, relieve the occasional and repeated attacks of senile vaginitis and dysuria which may develop years after the menopause has set in.

Estrogens, likewise, have proved useful in thickening and keratonizing the infantile and adolescent vulva and vagina and thus shortening the course of gonorrheal vulvovaginitis. Today this mode of therapy has been largely superseded by the quick action of sulfadiazine in curing gonorrhea.



Stilbestrol

Fig. 5.—The strong synthetic estrogen "stilbestrol" as depicted by Dodds.

Suppression of lactation may be effected by large doses of estrogens immediately post partum (5 mg. stilbestrol daily).

Recently a new and astounding effect exerted by the estrogens has been discovered. In adequate dosage, 5 mg. of stilbestrol daily, relieve the pain and may produce at least temporary regression of bone metastases due to carcinoma of the prostate. This antimasculinizing effect of estrogens has encouraged investigation of the effect of large doses of androgens for the relief of inoperable breast cancer in the female. Preliminary reports indicate that stimulation instead of regression occurs.

I have never been able to cure or even greatly palliate the symptoms of kraurosis vulvae, mainly a menopausal disease, nor obtained real or permanent relief of pruritus vulvae by means of estrogens. I shall not dignify by referring to them, the many and illogical other applications of estrogens which have been recommended.

For the treatment of the menopause symptoms, I recommend one mg. of stilbestrol by mouth, immediately before retiring. If taken with a small amount of food, the symptom of nausea rarely appears. Should nausea persist, we are forced to resort to estradiol tablets of which  $\frac{1}{2}$  mg., three times a day suffice. This drug is very expensive in comparison to the cheap synthetic estrogen. I have not given estrogens by hypodermic injections for many years. In the few patients who have claimed that oral treatment was ineffective, I have convinced myself by means of hormonal studies which show the disappearance of excessive gonadotropic factor from the urine, as well as by vaginal smears which become positive in response to the therapy, that the full drug effect was attained, and that the continuance of the symptoms might justly be ascribed to

profound psychic convictions due to the tales current among the patient's friends or to the injudicious remarks of the physician.

The introduction, subcutaneously of pellets, consisting of crystalline estrogen, is practicable but rarely indicated.

*Progestins.*—The corpus luteum hormone now is produced commercially by synthesis of steroids. This has somewhat reduced its cost. Progesterone is available for hypodermic use; pregnenolone for exhibition by mouth.

There are no reliable criteria for judging the effectiveness of this therapy in the human being. Endometrial biopsy is rarely convincing, particularly as the secretory phase has been shown to occur, at least in the monkey, in response to estrogens alone, although usually we ascribe the secretory phase to progestational, that is to corpus luteum action. Clinically, while I still employ both forms of the drug in the treatment of threatened abortion, in the prophylaxis of habitual abortion, and less often for the relief of dysmenorrhea, I am far from convinced of its efficacy. I emphasize this because the results are variable and inconclusive. They do not lend themselves to analysis. If employed, the dosage should be high, 10 mg. progesterone daily, or at least 40 to 80 mg. of pregnenolone.

In a recent case of universal alopecia in the female, prolonged subcutaneous injections of progesterone have been followed by a profuse regrowth of the head hair as well as of partial return of the eyebrows and cilia, without appearance of any labial hair growth.

*Androgens.*—Trial as well as a return to common sense has served to contract the field for application of androgenic therapy to within fairly well-defined limits. Available are oily solutions of testosterone propionate for injection, and tablets of methyl testosterone for oral use. Eunuchs, eunuchoids, and persistently infantile males who have passed the age of eighteen years are handicapped in their activities, in their ability to obtain employment, and in other spheres because of their beardlessness, high-pitched voices and asexual configurations. Some, at least temporary, relief of these deficiencies can be obtained by injecting up to 1,000 mg. of testosterone propionate during the course of seven to eight weeks, using a 50 mg. dose three times a week. Usually these patients develop some growth of beard, their voices deepen, redistribution of fat occurs, and a transient stimulation of libido supervenes. In consequence of this improvement, at least their self-assurance and self-respect increase.

Androgen therapy should not be employed either in retardation of growth, or in undescended testicles, as well as in males with Fröhlich's syndrome until their growth period has definitely been passed because of the regressive action of androgens exerted upon the testes. I might mention that huge doses of both estrogens and androgens fail to arrest growth in the gigantism of adolescence.

A temporary rejuvenation by androgenic therapy may result in aging males who have become listless, neurasthenic, particularly about their loss of libido, and who show a general let down, negligence, and weakness of memory. The effect, however, is so temporary that this therapy should be limited to very few and selected patients. Symptoms described as the "male climacteric," neurovascular and psychic, are uncommon. If actually present, they are transiently relieved by androgenic therapy.

Androgens are ineffective in the treatment of azospermia. I have convinced myself of this by prolonged control of semen specimens. The treatment of prostatic hypertrophy by means of androgens has been discontinued.

The antifeminizing power of androgens has been utilized in gynecology to relieve the excessive flow of menorrhagia and metrorrhagia, as well as to control the pain of dysmenorrhea. The effects can be obtained. They are temporary and purely palliative. Moreover, the dosage required approaches the threshold dose which produces masculinization so closely that in some instances permanent enlargement of the clitoris, hoarsening of the voice and hirsutism cannot be avoided. I therefore advise against this type of therapy.

*Adrenal Cortical Extracts.*—The last of the steroid hormones requiring consideration is adrenocorticosterone.

In Addison's disease, a patient may be maintained in good health for many years by the judicious use of adrenocorticosterone or/and adrenal cortical extract. The commercial extracts have proved entirely unsatisfactory. In some patients who respond gratifyingly over long periods of time to the crystalline hormone, occasional crises may arise, in which the intravenous use of an active extract, obtainable only from a few experimental laboratories, may be required for varying periods of time. Just as in diabetes, dietary supervision is obligatory. A low potassium, high sodium diet, bolstered by the giving of 15 grams of sodium chloride or sodium citrate additionally, is indicated. The supervision of this group, fortunately small in number when compared with diabetics, necessitates frequent and accurate laboratory control. Of these, electrolyte equilibrium and nitrogen balance determinations are essential. Therefore such patients should be entrusted to the care of physicians especially equipped for such studies. I have noted that premenstrually or during the menses, some women, suffering from Addison's disease, may temporarily require larger doses of hormone.

The implantation of pellets consisting of crystalline adrenocorticosterone involves the risk of sudden uncontrollable peaks of absorption, with consequent symptoms of acute hyperadrenalism, which may prove fatal to the already debilitated patient.

If a patient is to be subjected to operation for hyperadrenalism due to hyperplasia, adenoma or carcinoma of the cortex, she will require careful preoperative study, preoperative treatment, and especially the most meticulous postoperative supervision. In conditions of adenoma or carcinoma, the unaffected adrenal almost always has undergone "compensatory atrophy" if this descriptive misnomer can be used. The frightful postoperative mortality of adrenalectomy may be reduced if surgeons will call in the assistance of a medical man trained in this very special field or learn to employ the proper precautions themselves.

### Discussion

At the outset, I should have warned that of necessity my presentation would prove both eclectic and didactic. By now it will have been realized that unless specially emphasized, as in the tentative use of progesterone, I have limited my recommendations to fully authenticated and proved application of endocrine substances. To forestall many anticipated queries, covering particularly the field of functional conditions in the female, the treatment of which has harassed the entire medical profession



for years, I shall conclude my remarks by briefly touching upon the treatment of several of these syndromes. Let me warn once more, as I have done on many previous occasions, that a condition should not be diagnosed as "functional" unless sufficient evidence warrants such a conclusion. Such care will prevent some of the ludicrous errors I have encountered. I instance the giving of estrogens to girls with absent vagina in order to "cure" their persistent amenorrhea. Equally embarrassing to the physician was the persistent prescribing of thyroid for amenorrhea to a "virgin," whom he had known since infancy, up to her seventh month of pregnancy. I have seen repeatedly chorionic gonadotropin (which, by the way I repeat is ineffective) prescribed to control vaginal bleeding due to a tubal pregnancy.

*Amenorrhea.*—Unless resulting from remedial constitutional causes, such as obesity, hypothyroidism or malnutrition, amenorrhea does not respond to direct endocrine treatment. If a woman has a uterus, whether ovaries are present or not, she can be made to bleed. In amenorrhea, if 500,000 to 1,000,000 international units of estrogens have been given in the course of fifteen to thirty days, withdrawal bleeding will result, within five to ten days. Such treatments are valueless. A dose of only 30,000 international units given to a woman of seventy years will produce the same effect. This clinical experiment shows that in amenorrhea the threshold of response bleeding to estrogens is elevated. The cause of this elevation is unknown.

*Menorrhagia and metrorrhagia* can be of functional origin. Neither the gonadotropins, progesterone, nor estrogens are effective. Large doses of androgen temporarily arrest the bleeding but entail the risk previously referred to.

There is a small group suffering from puberty bleeding, adolescents whose basal metabolism falls to the minus twenty or lower levels. These girls respond promptly to thyroid medication and relapse if this treatment is stopped. This response appears paradoxical, for another hypothyroid group, more numerous than the preceding, suffering from amenorrhea, bleeds cyclically in response to the same medication. These two groups fully illustrate how little we as yet understand the mechanism of menstruation.

Consequently I resort more frequently today than previously to such nonendocrine remedies as ergot and curettage in younger patients, to x-ray and radium in older women, to relieve persistent and excessive bleeding.

*Dysmenorrhea.*—Dysmenorrhea remains a thorn in the side of both the general practitioner and gynecologist. These patients continue to wander from physician to physician, receive transient relief from any therapy and then soon relapse. Yet the majority of sufferers fundamentally are not neurasthenics although they may become so. Constitutionally, many are handicapped by infantilistic stigmas. The majority have a low threshold to pain. Some "outgrow" the condition, to use an old and homely phrase. Others are relieved by marriage, many more by parturition. A few reach the thirties unrelieved. Pregneninolone in doses of 20 to 40 mg., up to 80 mg. during a height of paroxysm, relieves some patients for a time. Estrogens give no relief. Our efforts must be to keep these patients from resorting to morphine. Codeine and atropine, to the point of tolerance, and coal tars remain our stand-by in the majority, and often insure relief. Dilatation under anesthesia and

the stem pessary give but temporary relief. The problem, though pressing, as yet remains unsolved. In the older group, x-ray castration should be resorted to.

In summary, I may state that in the majority of instances, where there is a deficiency of a given hormone, substitutional therapy proves effective. It is to be regretted that the vital function of the prepituitary can as yet not be replaced. The commonest error is that of employing hormones when no deficiency exists.

Overaction of the glands of internal secretion can be reduced by surgical means, adenoma of the thyroid, pancreas, pituitary and adrenal cortex may be instanced. Another method available is the use of x-ray therapy. Neither of these methods is ideal. As early as 1916, Hermann pointed out the antimasculinizing effect of estrogens. The interregulation and counteracting influences of the various glands upon each other were recognized by Eppinger, Falta and Rudinger in 1908, but only recently have attempts to utilize these actions been applied to clinical investigation. It is toward this goal that future research should be directed.

## Department of Reviews and Abstracts

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### Selected Abstracts

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#### Gynecologic Operations

**Adams, William M.:** Construction of an Artificial Vagina, Surg., Gynec. and Obst. 76: 746, 1943.

The author reports two successful cases of construction of artificial vagina, using a one-half thickness skin graft over a mold. He has introduced three innovations which are worthy. These consist of the use of three different types of molds. The first is made of sponge rubber, over which is placed a wire frame. The graft is glued to this with rubber cement. This is removed at the end of 10 days and replaced by a perforated plastic mold. The latter is worn for one week and replaced by a condom-covered rubber sponge, this being used off and on until no danger of contraction remains.

LT. L. M. HELLMAN, M.C., U.S.N.R.

**Koller, T.:** Therapeutic Pelvic Puncture in Gynecologic Disturbances, Schweiz. med. Wchnschr. 73: 374-377, 1943.

According to the author the therapeutic indications for the use of pelvic puncture are as follows: (1) Chronic inflammatory adnexal masses where prolonged conservative treatment fails to bring about improvement, and where operation is dangerous because of the risk of peritonitis. In these cases a pelvic puncture should not be done unless a more or less fluctuating mass is felt between the uterus and rectum. Recently in such cases, the author has instilled a sulfonamid preparation after emptying the abscess cavity; (2) Adnexal tumors with pelvic peritonitis and rapid exudation; (3) To differentiate between extrauterine pregnancy and chronic adnexal inflammation. In all of these cases there is no danger of infection from the procedure because infection is already present. The author warns against the use of pelvic puncture to empty follicle and corpus luteum cysts. In such cases it is safer to perform laparotomy. In rare cases, however, it is permissible to puncture an ovarian cyst through the vagina as for example in a woman so critically ill, that laparotomy is contraindicated.

The author has never observed any complications from pelvic puncture. In cases where pus is encountered, it is drained and nothing further is done. Where, however, blood, serous fluid or the contents of a dermoid cyst are obtained, an immediate laparotomy is done.

J. P. GREENHILL

#### Newborn Infant

**MacGregor, Agnes R.:** The Causes of Fetal and Neonatal Death, Edinburgh M. J. 50: 332, 1943.

The continuing high infant mortality rate of Scotland is rightly regarded as a national reproach to the medical profession of that country. So reports the author

who has made the determination of causes of these increased infant mortality rates a subject of special study at the Simpson Memorial Maternity Pavilion.

In a three-year period, 1939 to 1941, at the above institution, there were 7,523 live births, with 342 neonatal deaths, and 603 stillbirths, making in all 945 deaths. Of these, 338 liveborn and 422 deadborn children were examined post mortem, making 760 autopsies. The four principal causes of death for both groups include: (1) developmental malformations (142 cases) 18.7 per cent, (2) intracranial hemorrhage (277 cases) 36.4 per cent, (3) asphyxia (306 cases) 40.3 per cent and (4) infections (156 cases) 20.5 per cent.

The neonatal mortality rate per 1,000 live births was 45.5 for all infants (7,523 cases), 19.0 for full-term infants (6,815 cases) and 299.0 (708 cases) for premature infants. Expressed in another way these figures show that 9.4 per cent of all live births were premature which group contributed 62 per cent of the deaths, while the 90.6 per cent that were full-term births accounted for 38 per cent of the deaths.

The author has omitted from her list of causes of fetal and infant death such vague connotations as prematurity, atelectasis and thymic death. The writer reasons most logically that it is the development of pathological conditions that eventuate into fetal or infant death which must be considered rather than these so-called "half-diagnoses" which at most are but secondary contributing factors.

The writer concludes her article with a concise analysis of her findings encountered in each four main etiologic categories of fetal and neonatal death. She emphasizes, under infections, the frequently overlooked but peculiar susceptibility of the newborn infant to infection by common organisms of supposedly low virulence, e.g., the organisms of the *B. coli* group, in the first month, and especially in the first three weeks are often the cause of pneumonia and the most common cause of meningitis. Yet after the first month the *B. coli* group are virtually never found in either role.

CLAIR E. FOLSOME

**Guzman, V. G.: Intracranial Hemorrhage in the Newborn Infant, Obstet. y ginec. Latino-Americanas 1: 132-153, 1943.**

At the San Borja Maternity, Chile, intracranial hemorrhage accounted for 15.6 per cent of the newborn deaths over a period of eight years. Since 1939 there has been a decline in the number of newborn babies who showed signs of intracranial hemorrhage but who did not die. This is due to improved treatment of syphilis, better prenatal care and more careful conduct of labor, whereby unnecessary interference was avoided. During the last two years, vitamin K has been used prophylactically. The importance of congenital weakness and vascular fragility is supported by the fact that half of the babies who had cerebral hemorrhage weighed less than 2,500 grams. Responsibility for the intracranial hemorrhage can be attributed to the obstetrician in only 40 per cent of the cases. In the author's series intracranial hemorrhage was observed in 17.5 per cent of the babies delivered by the breech, in 10.7 per cent delivered by forceps and in 10 per cent delivered by internal version. The death rate of babies with cerebral hemorrhage is 77.4 per cent. Of the remaining 22.6 per cent some show evidences of injury to the nervous system late in life. There is no curative treatment for this complication hence prophylaxis is of the utmost importance.

J. P. GREENHILL

**Gavioli, Richardo L.: Fetal Ichthyosis, Arch. Clin. obst. y ginec. "Eliseo Cantón" 2: 134-142, 1943.**

The author reports a case with a study of the pathology. A premature female fetus, 35 cm. long, weighing 1,050 grams, displayed the characteristic signs of severe

ichthyosis; the hard skin, broken by deep lesions; the large immobile mouth, transversely oval; severe conjunctival inflammation which closed the eyes; atrophy of the fingers, nails, etc., and of the hands and feet and ears. The fetus survived 40 hours. Histologic study, as in other reported cases, revealed the typical lesions of epidermal hyperkeratosis and discrete lesions of dermal keratosis and fibrosis. The etiologic factor in this case may have been the consanguinity of the parents, who were first cousins.

J. P. GREENHILL

**Leon, Juan: Fetal Gigantism.** *Bol. soc. de obst. y ginec.* 21: 781-792, 1943.

The author reports a study by Alberto S. Coatz made in the Eliseo Cantón Clinic. Any fetus born weighing 5,000 or more grams was included in this classification. In 51,000 births, there were 125 cases of fetal gigantism (0.24 per cent), i.e., one in every 400 births. The maximum weight was 6,500 grams. Of the 125 cases, 54 of the mothers were Argentinians; the others foreigners. The age of the mother is not a factor in the etiology of fetal gigantism. Large infants seldom are born of primiparas; in this series 93 per cent of the mothers were multiparas, the majority secundiparas. There was no relation between fetal gigantism and the interval since the last pregnancy. The duration of menstruation was not an etiologic factor. Heredity undoubtedly plays a role in this type of case. Prolongation of gestation has an insignificant influence in production of large infants.

Excess eating by the mother can affect the infant, but this is not equal for all fetuses; hence individual factors must enter in, possibly dependent on fetal metabolism. The sex of the fetus has an important role, for twice as many male as female fetuses are gigantic. Hormonal influences, though not well understood, and fetal metabolism undoubtedly are important. Little value is attributed to the seasonal factor in the etiology.

Diabetes and syphilis are of but slight importance; in the 125 cases there was only one diabetic mother and three were syphilitic.

Current diagnostic methods, inspection and palpation, suffice to make a diagnosis of fetal gigantism. Simple radiography may clarify a doubtful diagnosis. A characteristic finding is fetal hyperflexion, necessitated by lack of space in the uterus.

Cephalic presentation is most common in these cases (91 per cent). Breech presentation occurred in 5.4 per cent and transverse in 3.5 per cent. Labor is prolonged in cases of fetal gigantism, particularly in multiparas. Spontaneous parturition occurred in 55 per cent of the primiparas and in 44 per cent of the multiparas. Operative interference was necessary in the remaining cases. From this it is concluded that fetal gigantism represents a serious complication in childbirth.

The puerperium was normal in 83 per cent; subfebrile in 10 per cent; febrile in 7 per cent. The maternal prognosis is serious but not dangerous. It is affected by the number of previous deliveries, dimensions of the fetal diameters, type of presentation, etc. The maternal mortality in this series was 2.4 per cent. The fetal prognosis is bad. The mortality in this series was 28 per cent and the fetal morbidity was extraordinary.

Prophylactic treatment consists in induced premature delivery. Cesarean section should be done in selected cases. At the time of delivery, the problem must be solved according to the type of dystocia. In cases of failure, embryotomy must be done.

J. P. GREENHILL.



### Complications of Pregnancy

**Harmon, Paul F., and Hoyne, Archibald: Poliomyelitis and Pregnancy, J. A. M. A. 123: 185, 1943.**

The authors report two cases of acute anterior poliomyelitis complicating pregnancy with fetal death occurring in one of the two cases, explained by the author as being due to fetal asphyxia as a result of a bulbar poliomyelitis. In order for infection to occur in the fetus, one would have to assume a blood stream infection passing through the placental barrier. There is no evidence that the virus of poliomyelitis is present in the blood stream with any degree of regularity if at all, and if it were, it would still have to be assumed that some irritant process was at work in the central nervous system of the fetus in order for infection to occur.

The conclusion of Kleinberg and Horwitz is quoted, "that pregnancy complicating acute anterior poliomyelitis may be anticipated to progress normally with a normal termination of labor and with a normal offspring." These latter authors found no evidence of intrauterine acute anterior poliomyelitis in 29 cases reported by them. They also concluded that there is no indication for interruption of pregnancy at any stage except for those reasons that would be operative in nonparalytic females. The passive immunity derived by the offspring from the mother does not persist for long, since a number of cases of acute anterior poliomyelitis under the age of one month have been reported.

WILLIAM BERMAN.

**Kapeller-Adler, R., and Cartwright, J. A. Vitamin B<sub>1</sub> and Toxemia of Pregnancy, Edinburgh M. J. 50: 305, 1943.**

The authors, concerned with previous reports in medical literature suggesting a relationship between vitamin B<sub>1</sub> deficiency and toxemia of pregnancy, determined to investigate the possibility of this purported etiological correlation.

Nineteen patients with mild or severe pre-eclamptic toxemia were treated with vitamin B<sub>1</sub>. The vitamin B<sub>1</sub> ("Benerva Roche" and "Berin") was administered both orally and intramuscularly. A normal course of treatment consisted of ten intramuscular injections of vitamin B<sub>1</sub>, 25 milligrams the first day and 10 milligrams on each of the succeeding nine days. In some instances the dosage was increased to 25 milligrams daily for the first four to five days. No beneficial effect was seen in any of these cases.

In the group of patients presenting severe pre-eclamptic toxemia the effect of vitamin B<sub>1</sub> treatment may even be described as detrimental. The authors contend that these results were to be expected taking into consideration the affinity of vitamin B<sub>1</sub> for histaminase. They conclude that the therapeutic use of vitamin B<sub>1</sub> in toxemia of pregnancy should be discouraged.

The authors substantiate their conclusions with careful biochemical analyses and close clinical observations which are well summarized in two tables and two graphic figures.

CLAIR E. FOLSOME.

**Davidson, L. S. P., Davis, L. J., and Innes, J.: Studies in Refractory Anemia. III., Edinburgh M. J. 50: 431, 1943.**

The authors in this article, the third section of their studies in refractory anemia, discuss a topic of considerable importance to obstetricians—the refractory anemia with hypercellular and megaloblastic marrow occurring in pregnancy and the puerperium.

In a summary of ten cases, followed for two years, the authors report that in all ten instances the anemia was severe. The hemoglobin readings ranged from 17 to 52 per cent during pregnancy or the puerperium with megaloblastic sternal marrow pictures. All the cases displayed temporary refractory periods varying

from two weeks to four months in spite of intensive parenteral liver therapy supplemented by the administration of iron and vitamin concentrates. In the majority of the cases repeated blood transfusions were necessary for the maintenance of life during the refractory period. Eventually complete recovery occurred in all cases.

CLAIR E. FOLSOME.

**Moscoso, Cesar Jacome: Eclampsia in the Quito Maternity, Bol. d. soc. de obst. y ginec. 21: 770-771, 1943.**

The author reports a statistical study of about 50,000 pregnancies observed at the Quito Maternity since 1910. His figures show a lower incidence of eclampsia than in other reported series. In 22,567 pregnancies during the last five months (the period when eclampsia develops) there were 80 cases of eclampsia, an incidence of 3.54 per 1,000. There was no indication that climate had any effect on development of eclampsia. In the dry season (5 months) there were 38 cases and in the damp season (7 months) 42 cases. Of the 80 cases of eclampsia, 47 were in primiparas (58.25 per cent); 11 in secundiparas; and 20 cases in later pregnancies.

The eclampsia occurred during pregnancy in 51 cases, during labor in 17 cases, and during the post-partum period in 12. Eight of the latter occurred within the first 24 hours after delivery, and in the others after 2, 3, 8 and 15 days.

In the 80 cases of eclampsia there were 29 maternal deaths (36 per cent). No reference to fetal mortality was noted in 9 cases; in the remaining 71, 30 died either before or after delivery (42 per cent).

In this series of cases both medical and surgical treatment was employed. Moscoso comments that since the mortality is higher than in most reported series, better methods of treatment must be found. He feels that improvement can be accomplished only by attention to the social factors and by educational measures. Many of the patients had not been seen prior to the development of severe eclampsia and had had no prenatal care.

The method of evacuating the uterus depends on individual circumstances and the condition of the patient. Other measures recommended include absolute quiet and avoidance of excitement; suppression of the eclamptic attacks by administration of morphine-chloral; maintenance of circulatory function; and bleeding to bring down arterial pressure. The last is contraindicated in the presence of anemia or imminent delivery.

J. P. GREENHILL.

**Caso, Rogelio and Baez, Juan Jose: Pregnancy, Parturition and Puerperium in Nephrectomized Patients, Bol. d. soc. de obst. y ginec. 21: 816-820, 1943.**

The authors report six cases. Four of the patients had nephrectomy for tuberculosis, one for pyonephrosis and one for lithiasis. In four women the pregnancy developed normally and was carried to term, with delivery of live fetuses. Three women had spontaneous deliveries and one required surgical intervention because of dystocia. In the other case, there was abortion of a dead, retained fetus. In one of the patients who ultimately had a spontaneous delivery, pyelitis developed during the second month of pregnancy. This was treated conservatively.

The authors conclude that three or four years should elapse after nephrectomy before pregnancy should be allowed, but this only if the remaining kidney is healthy. If the sole kidney is diseased, the pregnancy should be interrupted or sterilization should be carried out. The patient should have careful observation and study of renal function during the entire period of gestation. If there is any alteration in renal function which threatens the health of the patient, the pregnancy should be interrupted.

J. P. GREENHILL.

### Sterility, Fertility, Contraceptives

**Müller, J. H.** *The Significance of Hysterosalpingography for the Diagnosis and Treatment of Sterility*, Schweiz. med. Wchnschr. 73: 204-205, 1943.

In a group of 100 cases of sterility investigated by Müller, there were 64 cases of primary sterility and 36 cases of secondary infertility. In 46 per cent both tubes were patent, in 32 per cent both oviducts were closed and in 22 per cent only one tube was open. In a follow-up of 84 of the patients up to seven years, it was found that only 24 per cent of the patients became pregnant.

In 59 women no special therapy was carried out other than the hysterosalpingogram and 13 conceived. Hormone therapy was used in nine cases and three became pregnant. Ventrofixation was performed in 4 cases, tubal resections in 5, salpingostomies in 9, tubal implantation in 1, curettement in 5, and cervical dilatation in 2. Following these 25 operations only two women conceived; one after cervical dilatation and the other after unilateral adnexal resection and release of adhesions on the opposite side. This incidence of success following surgical operations, namely, less than 10 per cent agrees with the reports in the literature. The author believes that operation is justified in spite of the poor results because it will convince the patient that everything possible to overcome the sterility has been done.

J. P. GREENHILL.

**Rabau, E., Halbrecht, I., and Casper, J.:** *Endometrial Tuberculosis as a Cause of Sterility*, J. A. M. A. 122: 801, 1943.

The difficulty of the diagnosis of genital tuberculosis is stressed. There are very few clinical symptoms, and the diagnosis is usually accidental at either the time of operation or at the autopsy. A hypoplastic uterus is a frequent sign in genital tuberculosis. Methods for detection of genital tuberculosis that have appeared in the past literature are mentioned. The authors warn against salpingography as a means for diagnosing tuberculous salpingitis. They have used the endometrial biopsy method and they state that they have discovered a considerable number of cases of tuberculosis which had not given rise to any other sign or symptom. They found 20 cases of tuberculous endometritis in 208 endometrial biopsies studied for sterility. Tuberculous endometritis is quite compatible with patent tubes. The path of the infection of the uterine mucosa is uncertain. The authors feel that radical surgery should be reserved for only caseous processes.

WILLIAM BERMAN.

**Hamilton, W. J., Barnes, Josephine, and Dodds, Gladys H.:** *Phases of Maturation-Fertilization and Early Development in Man*, J. Obst. & Gynaec. Brit. Emp. 50: 241, 1943.

The authors present three early ova, one from a woman sterilized because of mitral stenosis; the second specimen from a woman sterilized because of a severe toxemia in her two previous pregnancies that resulted in miscarriages; and the third, from a woman who had a hysterectomy because of menorrhagia due to the associated presence of an ovarian cyst. From the history and the time of coitus, and the age of the specimen the authors conclude that ovulation occurs about  $14 \pm 1$  days before the beginning of the next period. There is some evidence from those few cases to show that the time of ovulation is more closely related to the beginning of the next menstruation than of the preceding one.

WILLIAM BERMAN.

**Ramos, Alberto Peralta:** Membranous Dysmenorrhea as a Factor in Sterility, *Obstet. y ginec. Latino-Americanas* 1: 117-131, 1943.

As emphasized by Alberto Peralta Ramos (Buenos Aires) membranous dysmenorrhea is important not only because it produces pain at the time of the menstrual flow but also because it causes sterility. Histologic study of the endometrium obtained in cases of membranous dysmenorrhea reveals that it is identical with that which is present during the last few days of the cycle except that it has not undergone autolysis. This is due to insufficient action of the physiologic, proteolytic and anticoagulating ferments.

The greatest pain in cases of membranous dysmenorrhea occurs just before and during menstruation when there is present the greatest amount of estrogen and the smallest amount of progesterone. The treatment recommended by the author is the use of gonadotropic hormones assisted by progesterone. In the future he intends to employ dehydrated plasma of pregnant women because this substance has yielded good results in some cases of menstrual irregularities.

J. P. GREENHILL.

**Westman, A.:** The Mechanism of the Transit of Ova in Women Observed During Laparotomy, *Schweiz. med. Wehnschr.* 73: 145-148, 1943.

Only a few operators have been fortunate enough to observe rhythmic contractions of the Fallopian tubes at the time of operation. However, as the author points out, with the Rubin apparatus tubal activity is, of course, registered on a kymograph. Mickulicz-Radecki studied the behavior of the tubes and ovaries in various phases of the menstrual cycle and found that at the time of ovulation the abdominal ends of the tubes came into intimate contact with the ovaries by means of activity of the tubes. Westman had previously shown that such a phenomenon takes place in many of the lower and higher mammals. This author also studied the mechanism of the transport of ova in women. At the time of operation he injected drops of lipiodol into the tunica albuginea and subsequently studied the position of the ovaries by roentgenography. He performed hysterosalpingography and thereby was able to study the relationship of the tubes to the ovaries. Serial roentgenograms showed that not only do the tubes possess motility but also the ovaries. The latter can move not only cranialward and caudalward but also on their long axis. This motility is brought about by contraction and relaxation of the smooth muscle in the ovarian ligaments and in the walls of the ovarian blood vessels. Roentgenograms showed that periodically the tubes bend around and encircle the ovaries. By means of this mechanism the expelled ovum is transported directly and quickly into the Fallopian tube.

J. P. GREENHILL.

**Rochat, R. L.:** Sterility of Ovarian Origin, *Schweiz. med. Wehnschr.* 73: 208-210, 1943.

According to the author the causes of sterility in the female may be divided into three groups: (1) Incapacity of the ovaries to produce ova or at least fertilizable ova; (2) Functional or chemical abnormalities in the genital tract which cause the death of spermatozoa or which prevent their union with ova; and, (3) Mechanical obstacles which prevent the union of sperm with ova. The second and third causes are easy to determine but the first is not. Likewise, whereas it is easy to detect abnormalities of spermatozoa by direct examination, this cannot be done with ova.

To determine the ovulatory function of the ovaries, two procedures are available namely, biopsy of the endometrium during the premenstrual phase, and a study of the temperature curve.

Ovarian dysfunction cannot be overcome by ovarian hormone therapy. But the author believes that a very satisfactory form of treatment is homotransplantation of an ovary. Such a transplant can act as a stimulant to a woman's defective ovaries and produce maturation of follicles. The author observed two pregnancies following homoplastic ovarian transplants in cases of hypofunction of the ovaries without apparent lesions.

A second form of treatment which may be satisfactory is the use of pituitary hormone. However, the urinary gonadotropins are not effective but the gonadotropic hormones derived from serum can produce maturation of follicles in women. At present since such gonadotropic hormones cannot be obtained, the author is resorting to blood of pregnant women because it contains a large amount of prolan A and B.

J. P. GREENHILL.

**Reist, A.: The Therapeutic Significance of Tubal Patency Tests,** *Schweiz. med. Wehnschr.* 77: 206-208, 1943.

During the last 16 years Reist performed Rubin tests on 381 women and found the tubes closed in 127 or 33.5 per cent. Among the 254 women who had patent tubes, 75 or 29.5 per cent became pregnant. Of this group 69 women gave birth to living children, 4 had miscarriages and 2 had extrauterine pregnancies. In 13 per cent of the 254 cases, pregnancy immediately followed the tubal patency test. Hence the Rubin test is not only a diagnostic procedure but also a therapeutic one.

There is no unity of opinion concerning why the Rubin test leads to pregnancy in so many cases of sterility. The reasons advanced are: (1) The test produces an increased activity of the tubes; (2) Mild adhesions are broken down; and (3) Reist believes that the test in some cases produces an additional ovulation in the premenstrual period; (4) Rubin tests help ascent of spermatozoa.

The author is in favor of performing repeated tubal patency tests at intervals of 2 or 3 months. His maximum for one patient is 12 tests.

J. P. GREENHILL.

**De Moraes, A., and Rosado J.: Hysterosalpingography in the Diagnosis of Ectopic Pregnancy,** *Obst. y ginec. Latino-Americanas* 1: 19-32, 1943.

The authors employed hysterosalpingography in cases of ectopic pregnancy at the A. de Moraes Maternity Hospital (Rio de Janeiro). In all the cases operation confirmed the diagnosis. The authors emphasize that the injection of oil is unnecessary in the cases of ectopic gestation complicated by rupture and internal hemorrhage but this aid is of great value in doubtful cases. Hysterosalpingography is of greatest diagnostic value in the cases of unruptured tubal pregnancy. This method in the opinion of the authors is harmless and less dangerous than pelvic puncture, biopsy of the endometrium, pneumonoscopy or pneumoroentgenography. The procedure is particularly useful in differentiating between a uterine angular pregnancy and an ectopic pregnancy.

J. P. GREENHILL.

**Scherer, H.: What Does Salpingography Accomplish in the Recognition of and Treatment of Female Sterility?** *Schweiz. med. Wehnschr.* 73: 147-149, 1943.

During the last 5 years the author employed salpingography in 80 cases of sterility. In this group there were 55 instances of primary sterility and 25 cases of secondary sterility. The causes of sterility were as follows: unilateral tubal closure 31.2 per cent, bilateral tubal closure 32.5 per cent, uterine hypoplasia 12.5 per cent and uterine malpositions and malformations 7.5 per cent. In 16.3 per cent of the cases no cause could be found.



Ten women (12.5 per cent) became pregnant within the first six months after the salpingography was done.

J. P. GREENHILL.

**Palazzo, O. R.: A New Hysterographic Method, Arch. Clin. Obstet. y. gynec. 1: 460-466, 1942.**

Palazzo recommends a new method for securing hysterograms. He uses a canula at the end of which is a small balloon. After insertion into the uterus the balloon is distended with lipiodol so that after complete distention, the entire outline of the uterine cavity may be readily outlined on an x-ray picture. In this way no lipiodol escapes into the tubes or into the peritoneum. Furthermore, the author considers it beneficial that none of the lipiodol is wasted.

J. P. GREENHILL.

### **Anatomy, Anomalies, etc.**

**Hirsch, Edwin F., and Martin, Mary E.: The Distribution of Nerves in the Adult Human Myometrium, Surg., Gynec. & Obst. 76: 697, 1943.**

The distribution of nerves in the myometrium was studied in normal nulliparous human uteri by cutting serial sections and staining with selective stains. The nerves of the inner portion of the myometrium extend through the muscle and connect with the radial arteries. Large nerve trunks also enter the endometrium. These contain both myelinated and nonmyelinated fibers. Sensory and organs similar to pacinian corpuscles were found in the crevices of the muscle tissues, and more particularly in the adventitia of branches of the uterine artery.

L. M. HELLMAN.

**Gray, Jessie: Successful Removal of a Sacral Parasitic Fetus, Canad. M. A. J. 47: 520, 1942.**

A newborn infant with a sacrococcygeal teratoma is described. The incidence of this complication is estimated to be between one in 20,000 to 55,000 births. A prenatal x-ray was obtained because it was thought that two fetal heads were palpable.

CARL P. HUBER.

### **Abortion**

**Dingle, Phillis: Two Cases of Renal Failure Following Abortion, J. of Obst. & Gynaec. Brit. Emp. 50: 246, 1943.**

The author describes two cases of oliguria following abortion. One case had a severe pre-eclamptic toxemia, in whom the added trauma of induced delivery brought about shock and kidney dysfunction. The second case was that of a patient who fell, and probably had a traumatic accidental hemorrhage, which produced hematuria, shock and oliguria with azotemia. A recent survey of the literature lends weight to the fact that the etiology may be due to a damaged placenta.

WILLIAM BERMAN.

**Paine, Alonzo K.: Progesterone in the Treatment of Threatened Abortion: A Review, Bull. New England M. Center 33: 39, 1943.**

In a brief but timely article on the use of Progesterone in the treatment of threatened abortion, Dr. Paine calls attention to the extremely shaky evidence

upon which such therapy is based. The use of this substance for the prevention of threatened abortion presupposes that its action is to inhibit uterine contractions. While such may be the case for isolated muscle strips, it cannot be conclusively demonstrated by the uterine bag technique. The nullifying action of progesterone on pituitrin induced contractions, the author feels, is only of indirect value as far as the abortion problem is concerned. With experimental evidence, either negative or inconclusive, one is forced to examine the clinical evidence. At the onset there is some confusion as to the definition of threatened abortion, with a perfectly conceivable chance for error even if the most rigid criteria are adhered to. Dr. Paine calls attention to the fact that the literature on the subject is remarkable because of a total lack of reports of clinical failure when progesterone is used. The series of cases reported are usually small, and one is impressed by the fact that frequently symptoms are so mild that hospitalization of the patients was unnecessary. The difficulty is always the lack of adequate controls. The question, what would have happened with no therapy? Or with sedation alone? The conclusion of the author is that progesterone in the treatment of threatened abortion is, in the light of present knowledge, of little if any value.

L. M. HELLMAN.

**Ludwig, F.: The Treatment of Imminent Abortion and Habitual Abortion With Corpus Luteum and Vitamin E, Schweiz. med. Wchnschr. 72: 1431-3, 1942.**

The author reviewed the reports in the literature concerning the use of corpus luteum hormone and vitamin E in the treatment of imminent and habitual abortion. He found that the treatment of habitual abortion with corpus luteum yielded 89.4 per cent success, the treatment with vitamin E alone 79.7 per cent and the combined use of corpus luteum and vitamin E gave 91.3 per cent successful results. The articles failed to state how many of the cases might have ended successfully without the therapy.

The reports in the literature indicate that in the treatment of imminent abortion, corpus luteum yielded 61.7 per cent success, vitamin E 83.3 per cent, combined corpus luteum and vitamin E 76.9 per cent and treatment without corpus luteum or vitamin E gave 71.2 per cent success.

The author himself obtained only 58.3 per cent success in his own cases treated with corpus luteum and vitamin E. This is in contrast to the 76.9 per cent reported in the literature. The author emphasizes that to accomplish any results, large doses of progesterone must be given. In cases of threatened abortion large doses must be given within a short period of time, but in cases of habitual abortion, the doses are divided over a long period of time.

J. P. GREENHILL.

**Brea, A. M.: Induced Abortion and Parturition by the Transparietal Uterine Route, Bol. Soc. de obst. y ginec. de Buenos Aires 21: 624, 1942.**

The author discusses induction of abortion by the methods of Boero and Aburel and reports 14 cases. The method of Boero consists of transparietal puncture of the uterus, and that of Aburel of the injection of a saturated solution of sodium chloride. The Boero method usually does not produce immediate abortion and thus permits stabilizing the condition of the mother before subjection to obstetrical trauma. The method of Aburel is effective from the third month to the end of gestation.

Brea concludes from his own experience that these two types of induced abortion have special indications; that they are very efficient in some cases; that they should be used only by specialists, because of the dangers in the hands of un-

trained physicians; that in special situations disaster may follow, as with all other methods. That is, the ideal method of inducing abortion which does not have inherent dangers has not yet been found.

J. P. GREENHILL.

### Mammary Glands

**Greene, E., and Caviedes, H.: Tuberculosis of the Breast and Its Coexistence With Cancer, Rev. méd. de Chile 71: 656, 1943.**

The authors present two cases of mammary tuberculosis, in one of which adenocarcinoma was present. A 42-year-old multipara complained of pain of a month's duration in the upper internal quadrant of the right breast, where a small mass was felt. Sulfathiazole relieved the pain but had no effect on the mass. Physical findings otherwise were negative except for a few small axillary glands and retraction of the nipple. The preoperative diagnosis was fibro-adenoma with probable malignant degeneration. The pathologist reported tuberculous lesions with intense nonspecific inflammatory infiltration as well as hyperplastic epithelial lesions and foci of adenocarcinoma.

A 27-year-old woman noted a tumor the size of a nut in the areola, painless, retracting the nipple. A course of ultraviolet light was without effect. Ten months later, during an attack of the grippe the lesion became painful, red, lustrous and tense, accompanied by bilateral axillary adenitis which suppurated. The primary lesion was opened and drained with fistula formation. The breast was later removed and diagnosis of tuberculosis confirmed.

The literature on the subject is reviewed. Tuberculosis of the breast is rare and its coexistence with carcinoma extremely rare. Treatment of tuberculosis early is medical in the rare case in which it is diagnosed. Simple resection of the breast and axillary glands is advocated for advanced cases by the authors.

ROBERT J. WEISSMAN.

**Müller, C.: Galactorrhea and Corpus Luteum, Schweiz. med. Wchnschr. 72: 1433-1434, 1942.**

A case of galactorrhea is reported by the author in which all therapy failed. Laparotomy was finally resorted to and at operation, a persistent corpus luteum was found and removed. The flow of milk ceased. The menses which had ceased during the period of galactorrhea, started again. At the time of the report one year had elapsed since the operation. The patient's menses remained regular and the flow of milk remained in abeyance.

The author questions whether, in view of the fact that amenorrhea is nearly always associated with extrapuerperal lactation, a persistent corpus luteum does not play an important role. There are many cases of extrapuerperal galactorrhea where a pituitary or ovarian tumor is found. In such cases since medical therapy does not help, it is advisable to resort to a posterior colpotomy to search for a persistent corpus luteum.

J. P. GREENHILL.

**Tolosa, Benedicto P. M.: Surgical Treatment of Puerperal Mastitis and Paramastitis, Rev. de ginec. y obst. 36: 157-173, 1942.**

Benedicto P. M. Tolosa avoids the disadvantages of both small and large incisions by using the electric or Paquelin cautery. With the tip of the instrument heated to nearly white red, the site where the fluctuation is best perceived is punctured by a rapid stroke: several strokes may be needed to reach the abscess

when the wall of interposing tissues is thick. If the patient is not pusillanimous, anesthesia is not necessary because reapplication of the cautery does not cause great pain: the local nerve endings are destroyed at the first contact. An imperative precaution is not to leave the tip of the cautery in the tissues for any length of time: the spreading heat would destroy more tissue than necessary, and this would delay healing. The only aftertreatment needed is renewal of the dressing twice a day and gentle evacuating massage.

Thirty cases, mostly of parenchymatous mastitis, were treated in this manner: all started to heal in a few days and cicatrization was complete in two weeks. The esthetic result was excellent.

J. P. GREENHILL.

### Malignancies

**Vespasiano Ramos, A.: Colpocytology As a Method of Diagnosing Cancer of the Uterus, An. brasil. de ginec. 15: 453-462, 1943.**

The author gives a minute description of the normal cytology of the vagina and of the different types of cells identified by Papanicolaou and Traut as pathognomonic of cervical and body carcinoma. He emphasizes the simplicity of this procedure and its great convenience especially at the age when cancer is common. Lesions can be discovered at a time when the possibilities of therapeutic success are great.

J. P. GREENHILL.

**Jones, Howard W., and Jones, Georgeanna E. Seegar: Panhysterectomy Versus Irradiation for Early Cancer of the Uterine Cervix, J. A. M. A. 122: 930, 1943.**

The authors compare 704 patients treated at the Kelly Clinic with radium or x-rays or a combination of the two, with 36 cases treated by radical hysterectomy. The absolute cure rate for those operated upon was 41.6 per cent and that for the radiation cases was 57.5 per cent. These two groups are compared with reference to both clinical stage, and microscopic grading according to the method of Martzloff. Considering all stages of carcinoma, irradiation of the spinal cell cancers gives the poorest results. There is also reason to believe that adenocarcinoma of the cervix is the most favorable type for operation. In conclusion the authors state that "irradiation will prove more satisfactory for the entire squamous cell group, including the accidentally discovered and preinvasive lesions."

WILLIAM BERMAN.

**Harvey, Roger A., and Ritchie, Robert N.: Carcinoma of the Cervix Complicated by Complete Procidentia, Radiology 41: 48, 1943.**

The authors review the literature of the treatment of cancer of the cervix in procidentia and stress the value of radiation therapy in this condition especially where surgery is contraindicated. They review one of their own cases in an 81-year-old white female treated with radiation alone. It is felt that in tumors of this type, the use of small and controlled doses of roentgen rays will combat the infection, reduce the size of tumor, and thereby make it easier and more advantageous to use subsequent radium therapy. There seems to be some relief or cure of the procidentia by radiation therapy. In younger women and in any cases with evidence of extension of carcinoma, roentgen therapy to the exteriorized tumor should be followed by a full course of roentgen therapy to the pelvis and radium insertion for 5,000 to 6,000 milligram hours.

WILLIAM BERMAN.

**Stromme, William B., and Traut, Herbert F.: Mesonephroma or Teratoid Adenocystoma of the Ovary, Surg., Gynec. & Obst. 76: 293-299, 1943.**

Since the original report of Schiller in 1939, only 30 instances of mesonephroma of the ovary have been reported. To this the authors add ten cases in the present communication. The ages of the patients in the present report varied from 11 months to 68 years, however the majority were over 30 years of age. In eight cases the tumors were located in the left ovary. They varied from three to seventeen centimeters in the smallest diameter and on section presented multiple small cysts. The solid portions were pinkish-gray in color. The cysts yielded a shiny mucoid material.

The tumors were all slow in rate of growth and the usual complaints of the patients were related to a developing abdominal mass. Spread was by way of direct implantation of papillary structures, or by way of the lymphatics. The finding of abdominal fluid was rare; however, extensive bowel implantations were found. The more differentiated tumors were made up of closely packed structures resembling acini. The less differentiated they became the more the papillarity increased.

The authors were unable to demonstrate anything resembling a glomerulus and this fact has led them to disagree with Schiller in regard to the Wolffian duct origin of these tumors.

Six of the ten patients were dead within a year after operation. Neither surgery nor x-ray appeared to alter the course of the diseases.

F. M. HELLMAN.

### Cesarean Section

**Sosa, Angel I., y Sanchez, and Nölting, David E.: Cesarean Section and Simultaneous Myomectomy, Bol. Soc. de obst. y ginec. de Buenos Aires 21: 808-816, 1943.**

The authors report 20 cases. In this group there were four deaths, one each from peritonitis, hemorrhage, collapse and shock and hemorrhage. When it is considered that cesarean section alone has a mortality rate between 1 and 2 per cent and postpuerperal myomectomy a rate between 2 and 4 per cent, it is immediately evident that the combination of these two procedures greatly increases the risks. Among the patients with pedunculated myomas, there were no deaths; but in those with intraligamentous growths, the mortality rate was 50 per cent.

From this experience and a review of the literature, the authors conclude that when a myoma is intramural or intraligamentous, and there is no ulceration or serious pressure on neighboring organs, cesarean section alone is the logical procedure. An exception to this can be made in the case of small or pedunculated myomas, where resection is simple, and in cases of generalized myomatosis, where hysterectomy is indicated. Although leaving the myoma increases the danger of necrosis or hemorrhage, this is compensated for by the immediate advantage of a more favorable postoperative course. Later another operation can be done to remove the tumor at a more favorable time for the patient.

The postoperative course of a woman subjected to cesarean operation is fraught with dangers due to the puerperal state, the effect of anesthesia, and of the operation itself because the uterine cavity is in communication with the abdominal cavity. These facts are substantiated by the morbidity and mortality statistics. If to these dangers are added those attendant on removal of myomas under conditions unfavorable for hemostasis and hence optimal for infection, it is easy to understand how the risks are multiplied.

J. P. GREENHILL.



### Gynecology

**Antunes, Altino, and Dutra, Lícínio H.: A Case of Brenner Tumor of the Ovary, An brasil de ginec. 7: 249-270, 1942.**

According to the authors the tumor was of the solid type and was found in a Negress, aged 30, with polymenorrhagia and a firm swelling of the ovary. This is the third case of Brenner tumor to be reported from Brazil, and perhaps from South America. Based on reports in the literature, the authors discuss the incidence of Brenner tumor, the age incidence, pathology, histogenesis, classification and clinical characteristics. Their own case confirms the concept that Brenner tumors are fibroepithelial and benign, devoid of hormonal function and of any influence on ovulation. Examination of the portion of the ovary which adhered to the tumor disclosed the existence of ovarian follicles at various stages of evolution, including corpus-albicans, although no corpus luteum was found. The patient, who was still sexually active, gave a history of 4 induced abortions, which fact indicated that the presence of the tumor did not inhibit fertilization nor development of the ovum.

J. P. GREENHILL.

**Lordy, Carmo: The Histogenesis of Walthard's Rests; Their Relation to Brenner Tumors of the Ovary, An. brasil de ginec. 7: 169-184, 1942.**

In reviewing a case which the author reported 13 years previously under the title "Islands of interstitial cells within a fibroma of the ovary," he found that he was dealing with the solid type of Brenner tumor of the ovary. The structural peculiarities of the epithelial nests, particularly the presence of cylindrical mucous epithelium in their innermost part, around the central lacuna, were in complete agreement with Meyer's criteria of Brenner tumors. Based on a review of the embryologic development of the human ovary and on the histologic examination of the cortex of the ovary from a newborn puppy, the author has been able to prove the complete morphologic identity between the cells derived from the third proliferation of the covering epithelium of the ovary and the cells constituting Walthard's rests, the similarity of which to the epithelial nests of Brenner tumors is generally conceded today. He, therefore, concludes that, most likely, Brenner tumors were derived from epithelial rests originating during the third proliferation of the germinative epithelium, just as the masculinizing tumors of the ovary originate from cells of the first proliferation. The author was also able to confirm the presence of the median groove in the nuclei of the epithelium—described by Danforth as characteristic for Walthard's rests and Brenner tumors—in both his own case of Brenner tumor and in sections of the ovarian cortex of the newborn dog. He believes that these linear depressions and all their variants conform with the line of cleavage of the nucleus and correspond to the various stages of direct or amitotic division of the cell.

J. P. GREENHILL.

### Fibroids

**Coghan, C. C.: Conservative Treatment of Multiple Fibroid Tumours; Successful Pregnancy After Enucleation of 64 Fibroid Tumours of the Uterus, M. J. Australia 1: 346, 1942.**

A cure is reported of a 24-year-old white unmarried female, upon whom myomectomy was performed. A total of 64 nodules, varying from  $2\frac{1}{4}$  inches to seedlings, were removed. Nearly 2 years later she was delivered of a living term-sized child by cesarean section. At the time of the second operation no mention was made of any recurrence of the myomas.

L. M. HELLMAN.

### Labor, Physiology, Management and Complications

**Vautrin, Guillermo:** Subcutaneous Symphysiotomy in an Incomplete and Complete Deflexion of the Head, *West. J. Surg.* 51: 389, 1943.

In this article there is revived the long debated value of subcutaneous symphysiotomy in obstetrics. The author reports 2 cases in which the operation was successfully performed under local anesthesia after very long labors. Failure to progress in these cases was due to incomplete deflexion of the fetal head. The technique of the operation is carefully described.

It is claimed that the anteroposterior diameter of the pelvis may be increased by 8 mm. The transverse diameter may be increased by 1 centimeter. One can expect spontaneous delivery in most cases following symphysiotomy and this occurred in the 2 cases reported. However, there is no contraindication to the use of forceps or pituitrin after the operation has been performed and the cervix is fully dilated. It is emphasized that immediate delivery after the operation is not necessary because the fetal heart often improves when the pressure has been relieved by symphysiotomy.

WILLIAM BICKERS.

**McConnell, Graham, and Schauffer, Goodrich C.:** Ergonovine by Vein During the Second Stage of Labor, *West. J. Surg.* 51: 403, 1943.

The use of ergonovine by vein during the second stage of labor is described. Various techniques in the management of the third stage, i.e., the use of posterior pituitary extract either before or after delivery of the placenta and the use of ergonovine following delivery of the placenta are compared with its routine use intravenously as the anterior shoulder engages under the symphysis. The chief objection raised against ergonovine, intravenously, as the anterior shoulder is being delivered is that incarceration of the placenta may ensue. The author emphasizes that this fear is rather exaggerated and that such anxiety should not precipitate hurried and unphysiologic methods of expression.

In the 142 cases studied, the average time between the intravenous injection of ergonovine and delivery of the placenta was 1 minute and 30 seconds. In the control group, using other techniques, the average time was 5 minutes and 40 seconds. Complications were few. Delayed post-partum hemorrhage occurred in 3 cases. One fatality occurred which could in no way be ascribed to the intravenous ergonovine. The administration of intravenous ergonovine is recommended in cesarean section.

WILLIAM BICKERS.

**Browne, Francis J.:** Reactions to Pressor Substances in Normal and Toxemic Women, *J. Obst. & Gynaec. Brit. Emp.* 50: 254, 1943.

The author studied normal women not pregnant (24 cases), normal pregnant women (20 cases), pregnancy with chronic hypertension (7 cases), and normal puerperal women (20 cases) with reference to the mean systolic rise in blood pressure after the injection of Tonephin (Bayer). The greatest increase occurred in the pre-eclamptic group (54 mm. Hg). It is felt that this may be due to a hypersensitivity characteristic of patients with chronic hypertension or of a woman who in later life will develop hypertension. A similar hypersensitivity is present in the patients with chronic hypertension especially where this hypertension existed before pregnancy. In pre-eclamptic toxemia, the reaction to the cold test was low, while in the hypertensives it was high. It was also noted that a high reaction was obtained in the puerperium of women who had had normal pregnancies. The cause of this increased sensitivity after delivery or its duration is not known.

WILLIAM BERMAN.

**Torpin, Richard: Fibromyoma of the Cervix Uteri Obstructing Labor, West. J. Surg. 51: 196, 1943.**

The author reports a case in which a 28-year-old white woman, para iii, gravida vi, was admitted to the hospital with the history of vaginal bleeding. On examination the uterus was found to be rigid and the diagnosis of premature separation of the placenta was made. Attempt to rupture the membranes failed because of an obstructing fibroid in the cervix, measuring 10 by 11 cm. A total hysterectomy was done using the method of primary ligation of the ovarian and uterine arteries. Pathological examination revealed a tumor arising from the cervix posteriorly, displacing the fetal head forward over the symphysis. A dissecting hematoma was found between the placenta and uterine wall. A classification for cervical fibromyoma is suggested.

WILLIAM BICKERS.

## Society Transactions

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### THE OBSTETRICAL SOCIETY OF PHILADELPHIA

*MEETING OF OCTOBER 7, 1943*

Case Reports: **Repeated Hydatidiform Mole Followed by Chorionepithelioma.** Eleanor H. Balph, M.D.

**Eclampsia, Cerebral Abscess and Hemorrhage.** S. Leon Israel, M.D., and Bernard J. Alpers, M.D. (by invitation). (For original article, see page 551.)

The following papers were presented:

**Carcinoma of the Cervix, End Results.** Charles A. Behney, M.D., and John Y. Howson, M.D. (For original paper, see page 506.)

**Biologic Characteristics of the Normal Vagina.** A. E. Rakoff, M.D., Louis G. Feo, M.D., and Leopold Goldstein, M.D. (For original paper, see page 467.)

*MEETING OF NOVEMBER 4, 1943*

Paper: **Gynecological Endocrinopathies of Early Life.** Emil Novak, M.D. (by invitation).

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### THE CHICAGO GYNECOLOGICAL SOCIETY

*MEETING OF NOVEMBER 19, 1943*

The following paper was presented:

**The Effect of the Interval Between Births on Maternal and Fetal Outlook.**

Nicholson J. Eastman, M.D. (by invitation). (For original article, see page 445.)

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### THE PITTSBURGH OBSTETRICAL & GYNECOLOGICAL SOCIETY

Regular meeting held Monday, October 11, 1943.

**The Voorhees Bag in Modern Obstetrics.** H. A. Power, M.D., and H. Erving, M.D. (by invitation). (For original article, see page 527.)

## Items

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### **The Passano Foundation, Incorporated**

The objects of the Foundation as set forth in its charter are: "For scientific and educational purposes, particularly to provide for scientific research and to publish the results of scientific research and to make awards for meritorious achievements in scientific research."

Dr. Emil Novak, Associate in Gynecology in the Johns Hopkins University Medical School is a director of the Foundation, also Dr. George Corner, Director of the Embryological Laboratory of the Carnegie Institution of Washington. Mr. Robert S. Gill, President of The Williams & Wilkins Company, has been elected President of the Foundation and Mr. George Hart Rowe, of The Williams & Wilkins Company is a director. Headquarters are at Mt. Royal and Guilford Avenues, Baltimore (2), Md.

Mr. E. B. Passano, for whom the Foundation is named, is Chairman of the Board of The Williams & Wilkins Company.

By the terms of the charter of the Foundation, the Board of Directors may inaugurate the establishment of an annual award not to exceed \$5,000 for the outstanding contribution to the advancement of medical science made within the year by an American citizen.

A number of other projects are under consideration. One is the advancement of postgraduate instruction among physicians in sections of the country not accessible to medical centers in the larger cities.

As indicated, the declared purpose of the Foundation is broad and consideration will be given to any activity within its limits.

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### **Color Films**

The motion picture in color, "Continuous Caudal Analgesia in Obstetrics," which was made available by Eli Lilly and Company, Indianapolis, for showing before medical societies and hospital staffs, has been in continuous demand since release several months ago. It was made at the U. S. Marine Hospital, Staten Island, by authorization of the Surgeon General, U. S. Public Health Service, and the demonstrations were carried out by Drs. Hingson and Edwards, originators of the technique.

The three films that were made at the Nutrition Clinic of the University of Cincinnati in the Hillman Hospital, Birmingham, Alabama, under the joint auspices of the Department of Internal Medicine at the University of Cincinnati and the University Hospitals of Cleveland have likewise been in constant circulation. One of these deals with thiamin chloride deficiency, the second with nicotinic acid deficiency, and the third with ariboflavinosis.

None of the films contain advertising. They are available to physicians for showing before medical societies and hospital staffs.

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### **American Board of Obstetrics and Gynecology, Inc.**

#### **Examinations**

The general oral and pathology examinations (Part II) for all candidates will be conducted at Pittsburgh, Pennsylvania, by the entire Board from Wednesday, June 7, through Tuesday, June 13, 1944. The Hotel William Penn in Pittsburgh



will be the headquarters for the Board. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Hotel.

Candidates for re-examination in Part II must make written application to the Secretary's Office not later than April 15, 1944.

The Office of the Surgeon General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

Deferment without time penalty under a waiver of our published regulations applying to civilian candidates, will be granted if a candidate in Service finds it impossible to proceed with the examinations of the Board.

Applications are now being received for the 1945 examinations. For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pa.

PAUL TITUS, M.D.

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## Necrology

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**H**ERMAN EMIL HAYD, M.D., F.A.C.S., M.R.C.S. (England), a member of the Advisory Editorial Board of the JOURNAL in its earlier years, Consulting Surgeon to the Memorial and Deaconess Hospitals of Buffalo, President of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons in 1911, died in Buffalo, where he had practiced his specialty and had been a resident for many years, February 18, 1944, at the age of 85.

## ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(*Appears in January, April, July, October*)

- American Gynecological Society.** (1876) *President*, George W. Kosmak, New York, N. Y. *Secretary*, H. C. Taylor, Jr., 842 Park Ave., New York, N. Y. Annual meeting Hershey, Pa., June 19-21, 1944.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, W. R. Cooke, Galveston, Texas. *Secretary*, James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 1944.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, John H. Moore, Grand Forks, N. D. *Secretary-Treasurer*, W. F. Mengert, Dallas, Tex. Annual meeting not announced.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President* Oren Moore, Charlotte, N. C. *Secretary*, T. J. Williams, University, Va. Annual meeting cancelled.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, L. E. Phaneuf. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Annual meeting Chicago, June 12-16, 1944.
- New York Obstetrical Society.** (1863) *President*, W. T. Kennedy. *Secretary*, R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, Catharine Macfarlane. *Secretary*, J. B. Montgomery, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, George H. Gardner. *Secretary*, Eugene A. Edwards, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, James P. McManus. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** *President*, Edward Friedman. *Secretary*, Carroll J. Fair, Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Layman A. Gray. *Secretary*, E. P. Solomon, Hegburn Bldg., Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, David B. Ludwig. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** (1861) *President*, Thos. Almy, Fall River, Mass. *Secretary*, Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.

\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the name is the year of founding.

- New England Obstetrical and Gynecological Society.** (1929) *President*, Frank A. Pemberton. *Secretary*, Fred. J. Lynch, 475 Commonwealth Ave., Boston, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, T. Floyd Bell. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.
- Washington Gynecological Society.** (1933) *President*, James R. Costello. *Secretary*, J. Keith Cromer, 1835 Eye St., N.W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, E. L. Zander. *Secretary*, R. A. Grasser, 2700 Napoleon Ave., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** (1924) *President*, S. A. Weintraub. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, R. Glenn Craig. *Secretary*, D. G. Morton, California University Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, T. F. Bunkley. *Secretary*, J. McIver, 714 Medical Arts Bldg., Dallas, Tex.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, Norman F. Miller. *Secretary*, Milo R. White, 2799 W. Grand Blvd., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** (1938) *President*, Edward C. Hughes. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May. Suspended for the duration.
- Alabama Association of Obstetricians and Gynecologists.** *President*, J. M. Weldon, Mobile, Ala. *Secretary*, Eva F. Dodge, Montgomery, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Carl M. Helwig. *Secretary*, Gerhard Ahnquist, 1336 Madison Street, Seattle. Meetings third Wednesday.
- Denver Obstetrical and Gynecological Society.** (1942) *Secretary*, Emmett A. Mechler, 1612 Tremont St., Denver, Colo. Suspended during war.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, Roland S. Cron. *Secretary*, Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, Geo. D. Huff. *Secretary*, Frank Russell, 233 A St., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, John D. Graham, Devil's Lake. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, A. L. Carson, Jr. *Secretary*, L. L. Schamburger, 628 State Office Bldg., Richmond, Va. Next meeting not announced.

